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Application Number 020707

PHARMACOLOGY REVIEWS

NDA 20-707

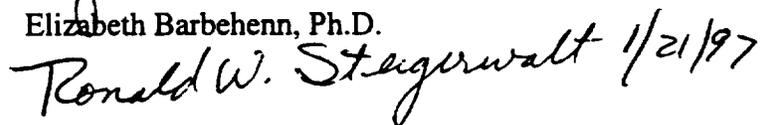
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Sanofi Winthrop, Inc.
Malvern, PA

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PHARMACOLOGY REVIEW OF NDA**DRUG:** Tiludronate disodium (Skelid^R); SR 41319 (acid form); SR 41319B (salt form)**DOSE:** 400 mg/day for 3 months followed by 3 months without drug**CATEGORY:** Anti-osteolytic (Paget's Disease)**RELATED DRUGS:** Alendronate (NDA 20-560); Etidronate (NDA 17-831); Pamidronate (NDA 20-036)


Elizabeth Barbehenn, Ph.D.



cc: NDA Arch
HFD-510
HFD-510/Steigerwalt/Barbehenn
Tiludron.NDA (.n#2)

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ADME: MICE (pp.2,3; RATS (pp.3-11), BABOONS (pp.11-16) DOGS (pp. 16, 22); RABBITS (p.17)	
1-YEAR TOXICITY BABOON (0,10,20,40 mkg; 9/s/g)	18
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ADME (assay) (vols 1.54 and 1.60): Plasma samples (0.2 ml) were spiked with internal standard, and then 25 ul (mouse assay) or 50 ul (human assay) of *blank human urine*, 100 ul 1 M *NaOH*, 100 ul 0.18 M *CaCl₂*, and 0.8 ml (mouse) or 1 ml (clinical) *d. water* were added, mixed, centrifuged, the solid residue dissolved in 150 ul EDTA/mobile phase solution, centrifuged again (in clinical assay) and 15 ul (preclinical) or 20 ul (clinical) were injected into the HPLC system. The range of standards utilized was 0.5 to 20 ug/ml (mouse) and 0.05-5 ug/ml (human). Samples were monitored at 269 nm. The recovery in human plasma was about 80% (vol 1.60).

Spiked rat plasma was used for mouse assay. "Female urine, morning miction", was recommended for better results. They use ultrapure water and Merck AR reagents, and then add 5% volume human urine which changes in composition each day.

	Limits of detection (LOD)		Limits of quantitation (LOQ)	
	Mouse	Human	Mouse	Human
Acid form (ug/ml)	0.04	0.01	0.10	0.05

Mouse Carcinogenicity Study (dosed fed; 4/s/g)

	MALES			FEMALES		
	wk 26	wk 52	wk 80	wk 26	wk 52	wk 80
control	0.00	0.00	0.00	0.00	0.00	0.00
10 mkd	0.00	0.00	0.00	0.00	0.00	0.00
25 mkd	0.00	0.00	0.00	0.00	0.00	0.00
60 mkd	0.00	0.00	*	0.00	*	*

*one/4 mice had measurable levels of parent drug

PK In Female Mice After One Oral Radiolabeled (14C) Dose (vol 1.54)

Drug, 50 mg/kg, given in *d. water* to fasted Swiss CD mice.

	Plasma	Blood
C_{max} (ug/ml)	15	10
T_{max} (h)	0.5	0.5
AUC (0-last)	17	13
t_{1/2} (h)	-	110
F (0-last) %	15	13

Excretion: 4% in urine and 76% in feces over 1 day

3% in urine and 85% in feces over 6 days.

Tissue Distribution Of ¹⁴C Tiludronate In Male F1C3H/C57 Mice

RS0005910426/02. Dose = 150 mg/kg (oral in d. water); whole body autoradiograms:
“Tissue distribution was characterized by high affinity for the skeleton (bone and cartilaginous tissues) and for the gastric and urinary bladder walls.”

ADME RAT**PK In Female Sprague-Dawley Rats (vol 1.54)**

RS0005920331/01. One dose of ¹⁴C tiludronate (50 mg/kg) to 8-wk old *fasted* rats (in d. Water).

RS0005950406/01. One dose of ¹⁴C tiludronate (50 mg/kg) to 1-yr old *fasted* rats (in d. Water).

	YOUNG RATS		OLD RATS
	Plasma	Blood	Plasma
C _{max} (ug/ml)	10	6	17
T _{max} (h)	0.5	0.5	1
AUC (0-last)	31	24	44
t _{1/2} (h)	-	65	41
F (0-last) %	11	9	5

(F= absolute bioavailability on basis of iv data)

YOUNG (Excretion)

4% in urine and 76% in feces over 24 hours

3% in urine and 85% in feces over 6 days.

OLD 4% urine and 88% feces over 6 days

TISSUE DISTRIBUTION: PEAK LEVEL COMPARISON (young vs old female rats)

RS0005950406/01. (Vol 1.54)

	Peak (¹⁴ C)Tissue:plasma Ratio (time of peak)	
	Young Rats	Old Rats
heart:	1 (24 hr)	0.2 (1 hr)
lung	3 (24 hr)	15 (8 h) and 9 (144 h)
liver:	6 (24 hr)	88 (144 hours)
kidney	80 (24 h)	160 (144 h)
femur	1,000 (24 h)	190 (144 h)

Tissue:plasma ratio increased with time in liver, lung, kidney, femur with both groups.

TISSUE DISTRIBUTION AND EXCRETION OF ¹⁴C-DRUG IN RATS

RA850890922/ML1. March 1985. Vol 1.56.

Three groups of Sprague-Dawley CD rats (6/s/g; 10 weeks old) were given by oral gavage in water, 12.5, 50, or 200 mg/kg/day for 14 days. On day 1 *only*, rats were fasted overnight before dosing; the remaining days, rats were dosed fed. Three/s/g were used to obtain PK data; 1/s/g were used for whole body autoradiography (30 um whole body sections of frozen tissue were freeze-dried and pressed against x-ray film); 5/s/g had samples of tissues counted. Blood levels were measured 2 hr postdose.

RESULTS:

Mortality: Six (One LD female with cause unknown; one MD male with blood in bladder; two HD males with stomach erosion; two HD females with blood in stomach and intestines)

Dose (mkd)	Urinary excretion (%)			Fecal excretion (%)		
	day1 (fasted)	day7 (fed)	day14 (fed)	day1 (fasted)	day7 (fed)	day14 (fed)
12.5	0.2	0.1	0.03	2	3	4
50	0.7	0.4	0.2	7	12	16
200	5	2	2	16	45	60

Dose	Mean blood level (after 14 days)
12.5 mkd	0.6 ug/ml
50 mkd	2
200 mkd	18

**TISSUE LEVELS (ug/g) TILUDRONATE IN RATS AFTER 2 WEEKS ORAL DOSING
14C-tiludronate (autoradiography)**

ORGAN	12.5 mkd		50 mkd		200 mkd	
	lived	died	lived	died	lived	died male, fem, female
heart	0.4	1.0	0.9	-	10	70, 200, 200
lung	0.5	0.9	2	2	10	130, 50, 400
liver	0.4	3	1	42	10	150, 400, 300
kidneys	0.6	18	2	4	20	500, 800, 700
stomach	0.4	23	3	12	10	500, 400, 1000
bladder	0.4	19	2	13	9	ND, 300, 80
spleen	0.8	54	4	4	25	70, 500, 600
adrenals	0.3	2	2	5	14	20, 300, 30
testes			0.8	3	5	20
apical femur	12	27	90	300	300	ND, 500, 600
median femur	9	12	70	100	200	ND, 400, 400

ND: no data

**FEMUR CONCENTRATION IN RATS AFTER 6 MONTHS TREATMENT (vol. 1.56)
RA850880727.**

Rats were given 0, 12.5, 50, or 200 mg/kg/day for 6 months by oral gavage in 10% gum arabic. Male and female values were very similar and were averaged. The femur was digested in HCl, filtered, and assayed by HPLC with UV detection at 265 nm (n=5-23).

Dose mg/kg/day	3 months (ug/g)	6 months (ug/g)
0	ND	ND
12.5	ND	10
50	90	150
200	1000	900

EXCRETION/ DISTRIBUTION (autoradiography in male rats) single iv or po dose
RS850850506. May 1985. (vol 1.56)

The salt (50 mg/kg iv and 150 mg/kg po; 100 uCi/kg) was administered in water. After treatment, some rats were placed in individual metabolism cages for 7 days to collect urine and feces (numbers of rats were not provided). At varying times postdose, between 1 h and 4 weeks, whole body autoradiography was done using 30 um whole body sections of frozen tissue, freeze-dried and pressed against x-ray film.

Results: Data were in the form of autoradiographs. They stated that **the drug was “distributed all over the organism except the cerebrospinal system... the main characteristic of the distribution was a short and medium term selective tropism towards bone tissue and the hyaline cartilage as well as the gastric epithelial mucosa.”**

EXCRETION OVER 7 DAYS (IV) OR 4 DAYS (ORAL)

	Urine	Feces
I.V. (50 mg/kg)	40%	5%
ORAL (150 mg/kg)	2%	96%

EXCRETION AND DISTRIBUTION IN FEMALE RATS OVER 28 DAYS (vol 1.56)
RS0005920327/01. 1991-1992

Eight female sprague-Dawley rats/group were given a single radioactive dose of the sodium salt (150 mg/kg orally or 50 mg/kg i.v.). Rats were fasted 16 hours before and 3 hours after dosing. Excretion (urine and feces) was monitored for 28 days in a sub-group of rats. **Whole body autoradiography** (30 um whole body sections of frozen tissue were freeze-dried and pressed against x-ray film). . Autoradiography was semi-quantitative (grey levels ranked) after optical density recorded by video camera.

EXCRETION

Urine and feces:

I.V.: Forty six % of radioactivity was excreted the first day, up to 60% by day 7.

Oral: 63% first day; 84% day 7

TISSUE LEVELS

Highest non-skeletal tissue levels:

I.V.: Kidney, liver, lung, spleen, blood

Oral: Gastric wall & kidney (up to 3 days postdose), followed by blood, liver lung muscle, spleen, brain

EXCRETION IN FEMALE RATS AFTER A SINGLE 50 mg/kg ORAL DOSE (vol 1.56)
RS0005910909/01.

Dose: 50 mg/kg [¹⁴C]-tiludronate.

	URINE	FECAL	TOTAL
Day 1:	4%	78%	82%
Day 2:	4%	85%	89%
Day 6:	5%	88%	93%

RADIOACTIVITY IN TISSUES AFTER ONE I.V. DOSE TO FEMALE RATS (vol. 1.55)
RS000590224/01. 1992.

A single i.v. dose of 12.5 mg/kg was given to fasted, 1 year-old female Sprague Dawley rats; rats were killed at times ranging from 0.5 to 144 hours. The % of dose was constant at 2% in the femur; 3% at 0.5 hours in the liver declining to a constant 0.3% between 5 and 6 days

AFFECT OF VEHICLE AND FASTING ON ABSORPTION IN RATS (vol 1.55)
RS850880726/CF1. 1986.

Sprague-Dawley rats were given 0 or a single oral dose of 50 mg/kg (gum arabic fasted or fed or d. water fasted or fed). Subgroups of 3/s were sampled from 15 min to 24 hours postdose.

	C _{max} (ug/ml)	T _{max} (h)	AUC ₀₋₂₄ (ug h/ml)	A _e (0-24) mg
gum arabic fasted	6	0.5	9.5	0.10
gum arabic fed	0.2	0.5	0.26	0.01
water fasted	12	0.5	20	0.18
water fed	0.7	0.5	0.37	0.011

TOXICOKINETICS OF ORAL ABSORPTION IN FASTING RATS

RS850860930/CF1.

Three groups of male and female rats were given a single oral 50 mg/kg dose in water (salt form) and divided as below:

group 1: free access to food

group 2: fasting from 20 h before until sacrifice

group 3: fasting from 6 h before to 2 h after

	Cmax (ug/ml)	AUC (ug h/ml)	Tmax (h)
free access to food	0.6	0.35	0.25 (M); 1 (F)
fasting 20 hours before dose	11 (M); 8 (F)	19 (M); 15 (F)	0.5 (M); 0.25 (F)
fasting 6 hours before dose	6 (M); 2 (F)	4 (M); 3 (F)	1 (M); 1 (F)

PRELIMINARY PK & DISPOSITION AFTER ORAL DOSING IN RATS (vol 1.55)

RS850831116/CF1. 1983.

Male Sprague-Dawley rats were given by oral gavage 100 mg/kg 14C drug.

Cmax (ug/ml)	3-9 (n=7)
Tmax (h)	0.5-1.5 (n=7)
AUC 0-8 h (ug h/ml)	8-16 (n=3)
RBC:blood ratio	9-50 (n=8)
% in urine (0-72 h)	2
% in feces (0-72 h)	95

RESIDUAL RADIOACTIVITY

(72 hours after a single 100 mg/kg dose (% of dose))

BLOOD	0.003
KIDNEY	0.009
INTESTINE	0.5
BONE	2.5

TOXICOKINETIC STUDY AFTER SINGLE ORAL DOSES TO RATS (vol 1.55)
 RS850860929/NV1. 1986.

Sprague Dawley rats (3/s/g) were given in 10% gum arabic single oral doses of SR 41319. Rats were not fasted; blood was collected 1 hour after drug administration.

DOSE (mg/kg)	Plasma levels (ug/ml±SD)
0	ND
12.5	ND
25	0.47±0.10
50	0.68± 0.16
100	1.0± 0.5
200	9.8± 5.7

ND= not detected

PLASMA LEVELS IN LOW DOSE RAT CARCINOGENICITY STUDY (vol 1.55)
 RS 0006910606/02. 1992. Lot 87/17.

Rats in the 2-year study had plasma sampled in 5/s/g during week 52 at 2 hours postdose in a satellite group. Drug was given in d.water. Rats were dosed fasted (food was removed early each morning at least 4 hours before dosing and returned one hour after completion of dosing). Immediately after dosing, 16 hour urine samples were collected from 5/s/g weeks 14, 27, 52, 79, 103. Drug levels were determined by HPLC with UV absorption.

DRUG WEEK 52 (5/s/g; unlabeled parent drug)

DOSE (mg/kg)	MALES (ug/ml)	FEMALES (ug/ml)
0	0	0
0	0	0
5	0	0
12.5	0.29± 0.49	0.11± 0.13
30	4.0± 1.5	1.7± 2.4

Human Cmax 3 ug/ml.

QUANTITATIVE TISSUE DISTRIBUTION [¹⁴C]tiludronate IN FASTED MALE RATS

(vol 1.55)

RS0005920226/03. 1991.

Male Sprague Dawley CD rats (3/g; 6 weeks old) were given one oral dose of 50 mg/kg in water of ¹⁴C tiludronate. Rats were fasted 16 hours before and 3 hours after dosing. Blood was taken at 0.5, 4, 8 hours and 1, 3, 7, 28, and 40 days postdose and plasma stored at -20..

Tissue samples were rinsed, dried, weighed, and stored at -20. Blood and tissue (50-150 mg) and plasma (200 mg) were digested in Soluene 350 and counted.

¹⁴C]tiludronate (ug eq free acid/g):

TISSUE	1 hr	4 hr	1 day	7 days	28 days
Stomach wall	330	25	1	3	NS
Duodenum wall	170	18	2	0.6	0.2
Jejunum wall	50	20	1	3	0.1
ileum wall	180	33	2	0.2	ND
femur	40	46	50	110	34
kidney	30	19	3	0.7	0.1
plasma	9	0.64	0.06	ND	ND
trachea	6	3	2	5	2
liver	3	1	0.28	0.6	ND

NS = no sample

ND = not detectable

QUANTITATIVE TISSUE DISTRIBUTION IN FEMALE RATS (vol 1.55)

RS0005920219/01. March 1991.

Female Sprague Dawley CD rats (3/g; 7 weeks old) were given one dose of 50 mg/kg in water of [¹⁴C]tiludronate. Rats were fasted 16 hours before and 3 hours after dosing. Blood was taken at 0.5, 4, 8 hours and 1, 3, 7, 28, and 40 days postdose. and plasma stored at -20.. Tissue samples were rinsed, dried, weighed, and stored at -20. Blood and tissue (50-150 mg) and plasma (200 mg) were digested in Soluene 350 and counted.

The highest levels of drug were in the kidney and scapula.

[¹⁴C]tiludronate (ug eq free acid/g):

TISSUE	1 hr	4 hr	1 day	7 days	28 days
Stomach wall	33 (0.4%)	27 (0.3%)	1 (0.01%)	0.1 (0%)	ND (0%)
Duodenum wall	13	27	1	0.2	0.3
Jejunum wall	19	20	1	0.2	0.1
ileum wall	28	24	2	0.3	0.1
femur	48 (0.6%)	34	57 (0.7%)	46	25 (0.3%)
kidney	54 (0.9%)	33	5 (0.1%)	0.37	0.1
plasma	21	0.7	0.06	ND	ND
trachea	15	7	6	2.8	1.7
liver	6	2	0.3	0.1	ND

NS = no sample

ND = not detectable

SINGLE ORAL DOSE (50 MG/KG [¹⁴C]tiludronate) TO FEMALE BABOONS (vol 1.58)

RS0005920429/01.

Four female, wild-caught baboons were fasted overnight and fed 3 hours postdose (50 mg/kg of ¹⁴C drug in d. water). Blood was collected from 0 to 144 hours (18 samples).

C _{max} (ug/ml)	15±9.5
t _{max} (h)	4.5±1.9
AUC(0-last)	140±84
Cl (l/h kg)	0.81±1
MRT (0-last) h	9.6±1.2
F (0-last) h	13

EFFECTS OF VEHICLE ON ORAL BIOAVAILABILITY/TOXICITY IN BABOONS

RA860860911. Sanofi, Montpellier, France. March 1986. Vol. 1.58.

Batch #: 85-07

TREATMENT: Four groups of baboons (*Papio papio*, 2/s/g except for control which had 1/s/g) were given by oral gavage 0, 10, 28, or 80 mg/kg/day for 7 days in d.water or 10% gum arabic. Animals found dead were necropsied. After treatment stopped, animals were observed to day 29.

RESULTS**MORTALITY:**

80 mg/kg: two females (#s 13 & 26; days 5 and 7; "drug-related")

28 mg/kg: one male (#20; "non-drug-related"; day 25).

CLINICAL SIGNS (drug-related deaths):

#13: prostration, decreased reflexes (gum arabic)

#26: prostration, decreased reflexes (d. water)

"non drug-related":

#20 prostration, decreased reflexes (d. water)

GROSS FINDINGS

#13: hematoma in pelvic abdominal cavity; clear liquid hydrothorax, pale kidneys, lungs congested and oedematous areas

#26: pale kidneys, pale heart with red spots on the mitral valve, non collapsed lungs with congested areas, stomach with thin wall and red spots on pylorus

#20: pale kidneys, pale heart with thick walls, non collapsed lungs with congested areas; stomach with thin wall and red spots on the mucosa but state that died from septicemia (multifocal purulent and septic lesions affecting heart, kidneys, lungs)

HISTOPATHOLOGY (#13 and #26): "imputable to SR 41319B" (tiludronate)

Extensive renal proximal tubular necrosis (acute with early regeneration in #13)

Massive lung edema with foci of septic purulent pneumonia (#26)

Areas of alveolar epicardiac edema with large area of acute pneumonia (#13)

Epicardiac edema in l. AV groove associated with edema (#13) and hemorrhage (#26)

Edema in mediastinum in both

Sponsor's analysis. These findings occurred previously:

RS860830901 (4-week study) one at 80 mg/kg died on day 6 with pulmonary lesions

RS860851126 (6-month study) one at 80 mg/kg died day 144 with pulmonary and renal lesions

"Therefore, the 80 mg/kg/d dose level is lethal for some animals only, whatever the vehicle used. These results are consistent with the great variability of plasma levels." (Vol.1.58; p.246)

EFFECTS OF VEHICLE ON ORAL BIOAVAILABILITY/TOXICITY IN BABOONS

BW/FC: No drug effect of treatment

CLINICAL CHEMISTRY: (day 8)

Creatinine: increased all treated but more so with d.water as vehicle

ALT: increased in individual treated baboons (gum arabic > d.water); all dose groups

LDH: increased in individual treated baboons

PK (DAY 1)

DOSE	Cmax (ug/ml)		Tmax (h)		AUC 0-24 (ug h/ml)	
	gum	water	gum	water	gum	water
10 mkd	0.8±0.4◁	7.2±3*	3.4±0.8	3.4±1.5	7.1±2.6	41±10*
28 mkd	7.3±2.5	14±3.5*	3.5±0.5	3.5±0.6	57±23	100±39
80 mkd	110±50	130±54	4.4±1.9	3.3±0.5	1100±710	1200±330

◁ Mean±SD

*p<0.05 vs 10% gum arabic

PK DURING 1-MONTH ORAL BABOON STUDY (vol 1.58)

RS0005902724/01. May 1991.

Two males and two females/g were given **40 mg/kg/day** by oral gavage in **d. water** for 1 month. Baboons were wild-captured, age unknown, but low bodyweight implying to Sanofi (not necessarily so, however) that they were young. They were fasted from 3 P.M. the day before until 2:00 P.M. the day after dosing (dosing was between 8-10:00 A.M.).

Parameter	day 1	day 8	day 29
tmax (h)	4	3	2
Cmax (ug/ml)	8.2	12	16
Cmin (ug/ml)	0	1	3
Cmean (ug/ml)	2.5	4.2	6.9
AUC 0-24 (ug h/ml)	60	100	170
Accumulation*	-	-	3

*AUC day 29/AUC day 1 (HPLC-UV assay; limit of quantitation: 0.8 ug/ml)

PK DURING 6-MONTH ORAL BABOON STUDY (vol 1.59)

RA850881005/CF1. October 1984; assayed February-November 1985.

Eight males and females/g were given, by oral gavage in 10% gum arabic, 0, 10, 28, and 80 mg/kg/day for 6 months with blood drawn from 2/s/g predose and two hours postdose for PK. Baboons were wild-captured, age unknown. They were fasted for 3 hours before dosing.

Dose	10 mkd	28 mkd	80 mkd
Day 48 t=0 hr	0.02*	0.19	2.8
t=2 hr	0.46	1.7	13
Day 104 t=0 h	0.05	0.34	1.5
t=2 h	0.4	2	10
Day 140 t=0 h	0.1	0.4	5
t=2 h	0.2	1	20
Day 190 t=0 h	0.2	0.4	3
t=2 h	0.3	2	19
MEAN VALUES	0.3	2	16

LOQ: 0.05 ug/ml; *ug/ml in 2/s/g

PK DURING 12-MONTH ORAL BABOON STUDY (vol 1.45)

RS0006910204/01. August 1986-1987.

Eight males and females/g were given, by oral gavage in d. water, 0, 10, 20, and 40 mkd. Baboons were wild-captured, age unknown; were fasted overnight before dosing. Plasma was collected before and 2 hours postdosing.

PLASMA LEVELS IN MALE & FEMALE BABOONS (ORAL) treatment phase (9/s/g)

	10 mkd		20 mkd		40 mkd	
	M	F	M	F	M	F
Day 35	2 *	2	6	4	13	13
Day 220	2	2	4	6	10	13
Day 280	2	1	3	4	6	8
Day 375	1	1	2	2	8	15

*ug/ml; 2 hours postdose (no data on AUC, tmax, Cmax, t1/2)

PK DURING 12-MONTH ORAL BABOON STUDY (vol 1.45)

RS0006910204/01. August 1987-1988.

Baboons (wild-captured, age unknown) were given, by oral gavage in d. water, 0, 10, 20, and 40 mg/kg/day. This is part of above study.

PLASMA LEVELS IN MALE & FEMALE BABOONS (3/s/g) (Recovery phase)

	10 mkd		20 mkd		40 mkd	
	M	F	M	F	M	F
Day 400	0.3 *	0.4	0.7	0.7	1	1
Day 478	0.2	0.3	0.5	0.6	1	0.6
Day 574	0.2	0.3	0.6	0.6	0.9	0.6
Day 764	0.0	0.0	0.04	0.05	0.0	0.0

*ug/ml (no data on AUC, tmax, Cmax, t1/2)

The data (not shown) between days 375 and 400 are peculiar: 1, 2, and 8 ug/ml (for males day 375) drop to 0.3, 0.7, and 1 ug/ml over the next 25 days; values are then stable until day 764 where again drug levels suddenly drop. Perhaps, this is due to the lack of sensitivity of the assay.

DRUG PROFILES AFTER A SINGLE IV OR ORAL DOSE (14C) IN MALE BABOONS

RA850891017/ML1. (vol 1.58)

One male baboon was given 22 mg/kg iv; another male was given 12 mg/kg orally in d.water. About 40% of the radioactivity was excreted in the urine when measured up to 72 h postdose (iv dosing); whereas there was about 6% in the urine (oral dosing).

EXCRETION OF 14C IN FEMALE BABOONS (ONE DOSE OF 50 MG/KG) (vol 1.59)

RS0005910913/01. December 1991.

Four female baboons (ages unknown) were given, by oral gavage in d. water, 50 mg/kg of [¹⁴C]tiludronate.

	EXCRETION		
	URINE (%)	FECES (%)	TOTAL (%)
0-24 h	2	60	62
0-48 h	3	74	77
0-144 h	3	80	83

Not reviewed: toxicokinetic data from the iv route

BABOON EXCRETION OF ORAL 14C TILUDRONATE (Vol 1.59)

RS0005910912/01

Single dose of 50 mg/kg to female baboons.

Urinary excretion over 6 days: 3%

Fecal excretion over 6 days: 80%

EXCRETION OF 14C DRUG IN FEMALE DOGS (50 mg/kg; single oral dose)

RS0005910911/02. 1991. (vol. 1.58)

Four female beagles were given 50 mg/kg 14C drug by oral gavage in d.water. The dogs were fasted overnight.

	URINE (%)	FECES (%)	TOTAL (%)
0-24 h	8	26	32
0-48 h	11	63	74
0-144 h	12	67	79

DRUG PROFILES AFTER A SINGLE ORAL DOSE (14C) TO FEMALE DOGS

RS005920702. May 1991. Montpellier, France. Vol 1.57.

Batch: CFQ6255

Four female dogs (16-19 months old) were given a single oral dose of 50 mg/kg in d. water.

Blood and plasma were analyzed up to 144 hours postdose. Dogs were fasted overnight, dosed in the morning, and fed in the afternoon.

	Plasma	Blood
Cmax (ug/ml)	16±5.4	12±6.4
Tmax (h)	1.1±0.7	1.0 ±0.7
AUC 0-last (ug h/ml)	110± 100	72 ±70
Cl (l/h kg)	0.7 ±0.4	1± 0.7
MRT (0-last; h)	5.0± 3.2	4.1 ±1.8
F (0-last; %)	5.7	8.0

RABBIT PK (SINGLE ORAL DOSE) (vol. 1.57)

RS0005920409. Female rabbits (18 weeks old) were given a single oral dose of 50 mg/kg in d.water. Rabbits were fasted overnight; time of next feeding not stated. Over 6 days, 0.7% was excreted in urine and 79% was in the feces.

Parameters	plasma
C_{max} (ug/ml)	3.5±2.7
T_{max} (h)	1±0.8
AUC (0-last)	11 ±8.5
CL (l hr/kg)	9.1±9.5
MRT (hr)	6.4±7.5
F (0-last) %	0.8

F= fraction absorbed

mean±SD (4/g)

ABSOLUTE BIOAVAILABILITY OF TILUDRONATE (2/24/93)

(radioactivity po/iv AUC)

Mouse 14%

Rat 9-11%

Rabbit 1%

Dog 6-8%

Monkey 11-13%

Human 6%

METABOLITES OF ¹⁴C TILUDRONATE IN ANIMAL MODELS (vol 1.59)

RS0005920730/01.

Data were collected from females (rats, rabbits, baboons, mice, dogs) on other chronic studies.

There was one major peak on UV which was parent; a second peak was thought to be a sulfoxide derivative.

PROTEIN BINDING: Tiludronate was bound 50-80% to serum albumin (rat, mouse, rabbit, dog, baboon). Binding was low affinity, limited number of sites producing, according to the sponsor, a large volume of distribution (p.139; vol 1.59).

1-YEAR TOXICITY STUDY IN BABOONS (vol. 1.45-1.47)

RS0006910204. August 1986- August 1987 (treatment) and 1987-1988 (recovery).

Sanofi Research, Montpellier, France (also reviewed 4/14/92).

Batch 86-12 (disodium salt)

TREATMENT: Four groups of Baboons from Senegal (*Papio papio*; 9/s/g; ages unknown but "young based on body weights" of 2.5 to 8 kg) were given 0, 10, 20, or 40 mg/kg/day by oral gavage in d. water for a year. The monkeys were fasted overnight. The last 3/s/g surviving baboons (only 2 HD females) were continued without drug for an additional year. Plasma PK by HPLC with UV detection at 280 nm.

Amendments to protocol (8/27/87): A radioscopic exam of long bone, rachis (spine), and abnormalities to be performed at completion of study on all animals. Bone densitometry on the right radius of each baboon (to be sampled during autopsy, cleaned and frozen at -20°). Left proximal tibial epiphysis to be sampled in formol, the right to be sampled in 70° alcohol; the left distal radial epiphysis to be sampled in formol, the left thumb first phalanx in formol.

Reversibility radiological exams at 2 weeks, 1, 3, and 6 months. "Femur not to be sampled for PK study. Radius sampled for densitometry study to be used." (p.29)

Protocol violations:

Submitted 12/5/96: Only one HD monkey (#66) had the spine examined; "appearance normal after 12 months treatment". PK data from the radius was not obtained because these bones were "first subjected to biomechanical tests which were destructive and precluded PK analysis". Not seen in report: data on thumb.

RESULTS

MORTALITY: 1 LD male, 2 MD females and 1 HD female. All were stated to have infectious lung diseases

CLINICAL SIGNS:

BODY WEIGHT: no drug effects

FOOD CONSUMPTION: "slightly lower in HD; reversible 6 weeks post treatment"

HEMATOLOGY, CLINICAL CHEMISTRY, EKG, HEMACULT:

"no drug effects"

URINALYSIS (*p<0.05):

	0	10	20	40	mkd
Creatinine (mM) female:	7.2;	8.1,	8.4,	11.5*	(day 184)
Sodium (mM) female:	21;	17,	32,	38*	(day 184)
Potassium (mM) female:	44;	53,	53,	64	(day 184) (N.S.; Large SE)
Potassium (umoles) male	9300;	8000,	8000,	16,000*	(day 184)
Calcium (umoles) male	680;	230,	180,	180	(Day 184)
	1800;	1500,	980*,	1400	(Day 366)
Calcium (umoles) female	190;	220,	110,	150	(day 184)
	940;	900,	1000,	600	(day 366)

1-YEAR TOXICITY STUDY IN BABOONS (0, 10, 20, 40 mkd; 9/s/g tx; 3/s/g recovery)**PATHOLOGY****ORGAN WEIGHTS:** values too variable to be useful (as %BW)**GROSS****BONE:**

Spontaneous unilateral rupture of the distal metaphysis at sampling in 3 HD (2 F & 1 M)

Right proximal radial epiphysis detached from diaphysis 1 HD M

Bone callus on the radius of 1 control F and 2 HD (M & F)

Petechiae on proximal tibial epiphysis: 1 MD F

Bones less hard at sectioning than for all other animals: 1 LD M and 1 HD F

Left tibia with wider diaphysis, congested periosteum, diaphyseal cavity reduced size: 1 HD F

STOMACH: Red areas on fundus mucosa in 2 HD M (recovery)

Numerous black spots on mucosa in 1 MD F (died)

Purplish fundus mucosa (1 HD F)

COLON: several to many red spots on mucosa 1 MD F and 1 HD M (recovery)**SKULL CAVITY** (abundant CSF): 1 LD F, 1 MD M, 1 MD F, 1 HD F (recovery)**HISTOPATHOLOGY (treated) 9/s/g****SPLEEN** (slight to marked lymphoid atrophy): 1 LD M, 2 MD F, 1 HD F (died or sacrificed)**HEART** (epicardiac edema of left AV groove): 1 LD M and 1 HD F (both died)**ESOPHAGUS** (focal erosions with inflammatory cell infiltration): 1 LD M and 1 MD F**LARGE INTESTINE** (lesions of esophagostomiasis): 4 LD, 2 MD, and 6 HD**PAROTID GLANDS** (chronic inflammation or serous dedifferentiation): 2 MD and 3 HD**TRACHEA** (inflammatory cell infiltration): 1 MD and 3 HD**MANDIBLE** (abscess with peripheral osteophytic reaction): 1 HD M**BONE** Distal Radial Epiphyses (tx) & Proximal Tibial Epiphyses (recovery)**Distal radial epiphysis** (examined in animals sacrificed after treatment. There were 6/s/g in treated.)**0 mkd (6/s/g)**

No findings

10 mkd (6/s/g)

Slight increase in thickness of spongiosae

5 M and 6 F

A few foci of epiphyseal growth plate processes in the spongiosae

1 M and 1 F

Decrease in osteoid and osteoblastic margins (slight)

5 M and 6 F

Slight decrease of subperiosteal bone resorption

1 M and 1 F

Increase in metaphyseal trabecular bone density and height

(v. slight to slight)

5 M and 6 F

1-YEAR TOXICITY STUDY IN BABOONS (0, 10, 20, 40 mkd)
BONE HISTOPATHOLOGY

Distal radial epiphysis (20 mkd; 6/s/g)

Moderate increase in thickness of spongiosae	6 M and 5 F
Foci or an area of epiphyseal growth plate processes in the spongiosae	3 M and 4 F
A few hypertrophic cartilage foci in the spongiosae	2 M and 2 F
Moderate decrease of osteoid and osteoblastic margins	4 M and 5 F
Slight to moderate decrease of subperiosteal bone resorption	6 M and 5 F
An area of epiphyseal growth plate processes in the spongiosae	3 M and 4 F
A few areas of hypertrophic cartilage in the spongiosae	2 M and 2 F
Increase in metaphyseal trabecular bone density and height (mod.)	5 M and 4 F

Distal radial epiphysis (40 mkd; 6/s/g)

Marked increase in thickness of spongiosae	6 M and 6 F
A few foci of epiphyseal growth plate processes in the spongiosae	0 M and 2 F
Foci or areas of hypertrophic cartilage foci in the spongiosae mainly at junction with trabecular bone	4 M and 6 F
Clean limit between spongiosae and metaphyseal trabecular bone	4 M and 6 F
Marked decrease of osteoid and osteoblastic margins	6 M and 6 F
Disappearance of subperiosteal bone resorption	6 M and 6 F

There was *no increase in metaphyseal trabecular bone density and height* (at 40 mkd) "due to a total inhibition of spongiosa remodeling (inhibition of bone resorption), leading to a clear limit between the spongiosa and the trabecular bone which was formed before the treatment started".

RECOVERY (3 s/g except only 2 HD females)

Proximal tibial epiphyses

There were few findings after one year without drug, but the bone examined was different from that examined in baboons after the treatment phase. In the one baboon where the distal radial epiphysis was examined, there was a moderate increase in height of the growth plate (a MD male).

NON DRUG-RELATED FINDINGS

LIVER granulomatous or chronic inflammatory foci: essentially all including controls
 LUNGS and TRACHEOBRONCHIAL LYMPH NODES (brown-pigmented macrophages):
 essentially all including controls
 LARGE INTESTINE (inflammatory cell infiltration): essentially all including controls

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EFFECT OF TILUDRONATE ON BONE HEALING IN MALE DOGS (Vol. 1.10)

RS0040921130/01. February to November 1992. Sanofi, Montpellier, France

Batch: 1SNL501

TREATMENT:

Expt 1: Four groups of male dogs (1-6 years old), had *sham surgery and no drug* (n=2), or had a *hemiosteotomy on the cortex of both ulnae* (n=4/g) and were given either 0 mkd (empty capsule), or 5 mg/kg tiludronate or 10 mg/kg etidronate. Dogs were dosed (capsules) starting the day after hemiosteotomy (between 8 and 9:30 am), fed at 1:30 pm and food withdrawn at 4 pm.

Expt 2: Two groups of male dogs (2-3 years old) had a hemiosteotomy and were treated either both before and after surgery (n=5) or before surgery only. Dose was 5 mg/kg for 5/7 days per week for 5 weeks before hemiosteotomy for both groups. Treatment was continued for 6 weeks after surgery for group 1 only.

The data were confusing for a variety of reasons:

Osteocalcin assays had a "technical problem"; the IGF-1 assay was "not validated".

Trabecular bone volume showed no changes; OV/BV and O.th (u) had SEMs too large to determine significance; the torsional stiffness test was not usable because most bones broke beside the fracture callus ("bone healing too advanced to be studied with this test"); there were only 2 dogs in control in expt 1 where stiffness and strength were measured.

In expt 1, one dog on tiludronate and one on etidronate "experienced a complete fracture of the ulna 10 days after hemiosteotomy (p.287).

The sponsor stated that, "Some of the results obtained in this study are difficult to explain.

Tiludronate triggered the replacement of woven bone by lamellar bone without a clear inhibition of bone resorption (expt 1). Tiludronate was more potent in decreasing bone turnover (expt 2) administered before hemiosteotomy only rather than when given both before and after.

Tiludronate should accumulate in the callus' woven bone decreasing osteoclast activity: such was not the case." (p.264)

OVARIECTOMY-INDUCED BONE CHANGES IN FEMALE DOGS (vol 1.11)

RS0040930120/02. Sanofi, Montpellier; INSERM, Paris;

March 1988-1992.

Batch: 88-20.

TREATMENT: Five groups of beagles (3-5 years old and 1-4 gestations) were given empty capsules (sham-operated; n=5), or were bilaterally ovariectomized (n=6/g) and given 0, 2.5, 5, or 10 mkd, in gelatin capsules, once daily for 3 months starting 1 week after surgery.

Treatment was followed by 3-months without drug. The cycle was then repeated once more.

Food was given 4 hours postdosing and withdrawn 3 hours later. Plasma drug levels were determined 16 hours postdose.

OVARIECTOMY-INDUCED BONE CHANGES IN DOGS (vol 1.11)**PLASMA DRUG LEVELS IN OVX DOGS (ug/ml)**

DOSE (mkd)	day 96*	day 279*
0 (sham)	ND	ND
0 (ovx)	ND	ND
2.5 (ovx)	ND	ND
5.0 (ovx)	Trace	0.07
10 (ovx)	0.2	0.2

Trace= 0.025 to 0.05 ug/ml.

*Day 96 is at end of first 3 months dosing; day 279 is at the end of the second 3 months dosing; Plasma was assayed 16 hours postdose.

Dogs had reduced trabecular bone volume and connectivity as well as few osteoid zones with active osteoblasts. At 10 mkd, osteoid zones were "very reduced, the osteoblasts present there were inactive and presented the morphology of border cells. No resorption lacunae or osteoclasts were observed." Unfortunately, the only PK data available is 16 hours postdose when essentially nothing could be measured (tmax is at 1 hour; p.445).

GENOTOXICITY (Vol 1.53)**SACCHAROMYCES CEREVISIAE; SCHIZOSACCHAROMYCES POMPE; V79 CELL RS860860430/JB1. April 1986.**

S. cerevisiae strain D5 was tested for effects on mitotic crossing over (both without and with hepatic microsomal enzymes); *S. Pompe* was tested for effects on forward mutation.

Tiludronate levels tested were 30 to 1000 ug/ml. The positive control (without S-9) was 15 ug/ml MMS; the positive control (with S9) was 3 mM cyclophosphomide. Tiludronate was negative \pm S9, but 1000 ug/ml is only 2.8 mM, about the same as the positive cyclophosphomide control. Solubility was given as the reason for the high dose, but no data were provided..

V79 cells (Chinese hamster embryonal lung cells; HGPRT locus): The test was negative up to 1000 ug/ml. The positive controls were 0.3mM MMS (-S9) and 2 mM DMN (+S9). However, there was minimal cytotoxicity (survival was 89% at the highest dose and 96% at the lowest dose) vs the recommended 10%-20% at the highest dose (40 CFR Ch. 1, 7/1/90 edition, §798.5300 and OECD guidelines); no data were available to substantiate limiting the high dose to 1000 ug/ml.

RAT HEPATOCYTE PRIMARY CULTURE/DNA REPAIR TEST (vol 1.53)
RS860830307/MM1. December 1982.

Batch: 82-01 (diluted in d.water)

TREATMENT: Tiludronate (14 and 1.4 nmoles/ml; batch 82-01) was tested in freshly-isolated rat hepatocytes incubated for 18-20 hours with ³H thymidine followed by an examination of slides for radioactivity over the nuclei, as an indicator of DNA synthesis as a result of DNA damage using autoradiographs. Positive controls were DMBA (10 nmoles/ml) and 2AF (1 nmole/ml). 50 ug/ml (but not 5 ug/ml) tiludronate was stated to be cytotoxic, but the data were not provided. Levels of 5 and 0.5 ug/ml (1.4 and 14 nmoles/ml) were used.

Quantification was by counting nuclear grains over viable cells. In the case of tiludronate, only 2 slides (20 nuclei/slide) were read for each concentration of tiludronate ("the third slide was unreadable"; p.322) vs the recommended 50 nuclei/slide (3 slides) be measured (Swierenga *et al.*; Mutation Res, 246, p.235, 1991). Doses appear to be low: even if 50 ug/ml were cytotoxic, dropping to 5 ug/ml as the high dose does not seem justified. The test was negative, as performed, but doses were low and too few cells were examined to be a valid test.

DRUG	NUCLEAR GRAINS	CYTOPLASMIC GRAINS
Water	11±0.4*	14± 0.6
Tiludronate (1.4 nmoles/ml)	19±0.9	26 ±1.2
Tiludronate (14 nmoles/ml)	25±0.9	29± 0.8
DMBA (10 nmoles/ml)	39±1.2	18± 0.7
2AF (1 nmole/ml)	106±3.4	23± 1.0

*Mean±SEM

DISTRIBUTION OF TILUDRONATE IN VIVO:**SINGLE DOSE STUDIES**

MALE MICE (whole body autoradiograms following single oral dose): **"Tissue distribution was characterized by high affinity for the skeleton (bone and cartilaginous tissues) and for the gastric and urinary bladder walls."**

MALE RATS (whole body autoradiograms following single iv dose): **"Tissue distribution all over the organism except the cerebrospinal system... the main characteristic of the distribution was a short and medium term (2 hours to 2 weeks) selective tropism towards bone tissue and the hyaline cartilage as well as the gastric epithelial mucosa."**

FEMALE RATS (whole body autoradiograms following single 50 mg/kg iv dose or single 150 mg/kg oral dose): Highest non-skeletal levels after IV dose: kidney, liver, lung, spleen, blood
Highest non-skeletal levels after PO dose: gastric wall, kidney, blood, liver, lung, muscle, spleen, and brain.

FASTED MALE RATS (solubilization of tissues following a single oral dose): The highest levels at one hour postdose were in the **walls of the gi tract** followed by **femur, kidney, and trachea**. There were no measurable plasma levels after 1 day. The walls of the gi tract had measurable drug levels out to 28 days for duodenum and jejunum; 7 days for rest.

FASTED FEMALE RATS (solubilization of tissues following a single oral dose): The highest levels at one hour postdose were in the **femur and kidney** followed by the **walls of the gi tract** and the **trachea**. The femur had constant levels (to 28 days) while there were no measurable plasma levels after 1 day. There were measurable levels in other tissues out to 28 days except for liver (measurable out to 7 days).

MULTIPLE DOSE STUDY:

MALE AND FEMALE RATS: (rats were dosed orally, fed, for 2 weeks at 12.5, 50, or 200 mg/kg and tissues counted. Levels in declining concentration were **femur, spleen, kidney, adrenal, lung, liver, stomach, heart, bladder, and testes**).

METABOLISM: No metabolites were seen (using the method of precipitation, solubilization, and HPLC assay with UV monitoring).

EXCRETION: 70-90% fecal after an oral dose with 2-5% urinary (for all species). After an iv dose, about 40% was excreted in the urine of rats.

HUMAN PK (Label and vols 1.86 and 1.94)

Paget's patients taking 400 mg/day (for 12 days to 12 weeks) had plasma levels 1-2 hours postdose ranging from 1 to 4.6 ug/ml. Tiludronate was 90% bound to serum albumin. The plasma t1/2 was 6 days; the bone t1/2 remains unknown (alendronate t1/2 was estimated to be 10 years). Plasma levels were higher in patients ≥ 65 years old. Instructions are to take tiludronate 2 hours before or after eating.

400 mg to healthy male subjects:

t_{max} 1-2 hours

C_{max}: 3 ug/ml

Absolute bioavailability was 6%.

Clinical efficacy: Serum ALKP reduced (main parameter)

Urinary OH-proline reduced

Number of osteoclasts: reduced (Vol 207)

Number of lytic lesions reduced

PREC LINICAL FINDINGS (BONE):

BAB00N (6-month oral study): 0, 10, 28, 80 mg/kg/day

(Compare PK data to human C_{max} of about 3 ug/ml)

HISTOMORPHOMETRIC STUDY

Dose	("C _{max} ")	Findings
0 mkd	(0.0 ug/ml):	no abnormalities
10 mkd	(0.3 ug/ml):	no abnormalities
28 mkd	(2 ug/ml):	increased thickness of primary and secondary spongiosa
80 mkd	(16 ug/ml):	SEE BELOW:

"...spongiosae were hypertrophic, osteoid and osteoblastic margins were very decreased, as was the osteoclastic population; there were islets of hypertrophic cartilage in the spongiosae indicating a defect in resorption, compacted areas or foci in the spongiosae characterized by fragmentation and disorientation of trabeculae often associated with a fibrous reaction, =microfractures"

"...slight morphological signs of osteomalacia indicating delayed mineralization were observed. The lack of increase in the osteoid volume in the baboons treated at 80 mg/kg/day, while mineralization was strongly reduced, suggests that this diphosphonate has a toxic effect on osteoblasts at this dose." P.J. Meunier and S. Charbon, Universite Claude Bernard, Laboratoire de Recherches sur l'Histodynamie Osseuse (vol 1.12, p.108)

BABOON (6-month oral study; 0, 10, 28, 80 mg/kg/day):

"...at the high dose, articular sequellae may occur in the form of epiphyseal slidings, exostoses, and possible malformations whose permanent or transient nature cannot be judged within a 4-month observation period." (radiological study; vol 1.12, p.19).

"After 6 months, ...accentuation of the initial condensation associated with a distal demineralization..." "...there is a likely association of a proximal hyperdensity and of a distal decalcification. After discontinuation of treatment, decalcification is overcorrected and the metaphysis becomes denser than the epiphysis." "On the 4th month (of recovery), the distal metaphysis returns to normal density. The apparent osteoporosis observed on the radiographs is probably only a relative hypodensity... However, after a 4-month reversibility, a non-homogenous densification of the proximal metaphysis still persists." *Pr. M. Laval-Jeantet, clinical expert* (vol 1.12, p.24)

Calcification rate was decreased in both cortical and trabecular bone.

No. Osteoclasts/mm² decreased

No. Osteoclasts/resorption surface area decreased

RADIOLOGICAL STUDY BABOON (after 6-months treatment): At 28 mkd and 80 mkd, there was increased radial metaphyseal density. Other abnormalities (in femur and upper tibia) these doses included the widening and irregular appearance of the epiphyseal growth plates described as "pseudo-rachitic". Reversibility was dose-related, but at 80 mkd, irregularities were still evident: insufficient bone remodeling and exostosis pattern (benign cartilaginous growth from bone in the femoral epiphyseal growth plate) after 4 months without drug.

The baboon C_{max} at the 80 mkd dose averaged 16 ug/ml vs 3 ug/ml for humans (or a 5-fold difference). There was a clear reduction of the osteoclastic population at 10 mg/kg/day "demonstrating an antiosteoclastic effect" with a C_{max} of 0.3 (0.1 the human C_{max}).

TREATMENT PHASE BAB00N (12-month oral study; 0, 10, 20, 40 mkd):**Distal Radial Epiphyses (6/s/g)**

Findings included the spontaneous unilateral rupture of the distal metaphysis at sampling in HD baboons, the detachment from the diaphysis of the right proximal radial epiphysis, bones less hard at sectioning, left tibia with wider diaphysis, congested periosteum, and diaphyseal cavity reduced in size.

Other findings in bone (increasing in extent and severity as function of dose) included foci of epiphyseal growth plate processes in the spongiosae, decrease in osteoid and osteoblastic margins, decrease of subperiosteal bone resorption, increase in thickness of spongiosae, increase in metaphyseal trabecular bone density and height (L and MD), and a clean limit between spongiosae and metaphyseal trabecular bone (HD). There was no increase in metaphyseal trabecular bone density and height (HD) "due to a total inhibition of spongiosa remodeling (inhibition of bone resorption), leading to a clear limit between the spongiosa and the trabecular bone". In L and MD groups, bone resorption was only partial.

RECOVERY PHASE BAB00N (12-month oral study; 0, 10, 20, 40 mkd):**Proximal Tibial Epiphyses (3/s/g except only 2 HD females)**

There were few findings after one year without drug *but the bone examined after the recovery phase (proximal tibial epiphysis) was different from that examined in baboons after the treatment phase (distal radial epiphyses)*. In the one recovery baboon where the distal radial epiphysis was examined, there was a moderate increase in height of the growth plate as seen after treatment phase (a MD male).

BONE STUDIES (RAT)

RADIOLOGICAL STUDY (12.5, 50, 200 mkd): Increased primary spongiosa at ≥ 50 mkd. At 200 mkd, there was irregular cartilage, significant increase of epiphyseal growth plate, and decreased cortical mineralization (vol 1.9 NDA).

BONE STUDIES (DOG)

OVX +/- DRUG: Ovariectomized dogs were treated with tiludronate for 3 months, followed by 3 months off drug (this cycle repeated once). Dogs had reduced trabecular bone volume and connectivity as well as few osteoid zones with active osteoblasts. At the high dose of 10 mkd, osteoid zones were "very reduced, the osteoblasts present there were inactive." The only PK data available is 16 hours postdose when essentially nothing could be measured (t_{max} is at 1 hour). On a mg/m^2 basis, the 10 mg/kg dog exposure was the same as human at the 400 mg/day dose. (vol 1.11; pp.445 & 455)

RATIONALE FOR FINDINGS:**PRIMARY SPONGIOSA FORMED DURING BONE GROWTH***

Retention of primary spongiosa results from a block in the bone remodeling process.

FIRST ARF SEQUENCE (replacing cartilage with woven bone)

The calcified cartilage septal matrix laid down by chondroblasts is partially resorbed by osteoclasts after which osteoblasts form a layer of woven bone on top. The trabeculae formed are called the *primary spongiosa* and is seen during growth of bones.

SECOND ARF SEQUENCE (replacing woven bone with lamellar bone)

The woven bone and cartilaginous remnants are replaced with lamellar bone to produce the mature state of trabecular bone called the *secondary spongiosa*.

R. Baron in "Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism", M.J.Favus, ed. Raven Press, NY, 1993. ARF= activation, resorption, formation.

It appears that the ARF process is partially blocked by tiludronate. For baboons, the blockage began at the lowest dose tested in the 1-year baboon study (Cmax 0.3 ug/ml or 1/10th the human Cmax) resulting at the higher doses in weakened bone. Rats had decreased cortical mineralization with inhibition of osteoclasts, chondrocytes, and osteoblasts. In dogs, the osteoblasts became inactive.

OTHER TARGET ORGANS (PRECLINICAL):**GI**

One major puzzle with bisphosphonates has been the gastritis seen after i.v. as well as oral dosing (dogs, rats, baboons). This phenomenon was seen with alendronate, also. However, tiludronate was shown to be localized in the *gastric epithelial mucosa* of rats after i.v. and oral dosing of a radiolabeled dose.

BABOON: Gastric erosions and acute ulcerative esophagitis were seen in 3/5 baboons given 80 mg/kg/day by oral gavage for 6-months.

RATS: There was significantly **reduced gastric emptying** after a single oral dose of 100 mg/kg. There was a dose-related **inhibition of histamine-induced gastric acid secretion** at 100 and 200 mg/kg i.d., although it did not reach significance because the control rats were too variable. Erosions and fibrosis in the stomach at several places throughout the glandular area of the stomach were seen at 50 mg/kg and above in a 6-month toxicity study. (Rev. 3/16/92; p. 23)

KIDNEY:

Baboon: Renal proximal tubulopathy in 3/3 baboons at 80 mg/kg/day (5x the human Cmax) (oral gavage in 6-month study; confirmed by EM).

Rat: Subacute or chronic proximal renal tubulopathy at 200 mg/kg in 14/14 rats (6-month gavage study in fed rats; no plasma PK data).

LUNG:

Baboon: congestion, edema, inflammatory infiltration in 3/5 at 80 mg/kg/day by oral gavage in 6-month study

Rat: pulmonary congestion with intraalveolar or perivascular edema and hemorrhage in a 6-month oral toxicity study.

HEART:

Rat: Prolongation of the QT interval at 50 and 200 mg/kg females in the 6-month study.

Baboon: Decreased heart rate, bradycardia, increased P wave, PR and QT intervals at 4x the human C_{max}. "ECG showed slightly altered heart rate, characterized by sinoatrial arrest, in several high-dose (80 mg/kg) animals...and two mid-dose (28 mg/kg) animals." (Vol 1.42, p.29) These doses represent 1x (28 mg/kg) and 5x (80 mg/kg) the human exposure (p.14 review).

Some weaknesses of the NDA submission:

Reproductive toxicity studies: Animals were dosed fed (not fasted) and gum arabic was used as the vehicle in the teratology studies (which further reduces absorption compared to d.water) . No data on exposure was obtained. The sponsor was requested (October 20, 1995) to do a study dosing female rats from before mating until four days post-partum (and to submit a protocol before beginning). They responded on October 10, 1996 stating that although there was no overt maternal toxicity at any dose, they based their MTD on uterine inertia at delivery (dystocia). However, this is not a true end-point, especially as it occurred in only 1/12 females in the fertility study and 2/22 in the peri/post natal development study. As a result, we do not have a full picture of reproductive toxicity. Furthermore, the calculations for teratogenicity were done on a fetal, and not a litter, basis, as required.

Carcinogenicity studies: Plasma levels were obtained 2 hours postdose in both mice and rats. Mice had essentially no measurable exposure at any time during the study, which was not surprising considering that they were given very low doses and dosed fed. Rats had plasma levels that were either undetectable (low dose), 0.1x the human C_{max} (mid-dose), or 0.5 to 1x the human C_{max} (high dose). There were no findings in these studies, but, again, there was essentially no exposure to drug. These studies were presented to the CAC (February 15, 1996), deemed not valid and are being repeated.

Genotoxicity studies: The following tests were negative: the Ames test, the *S. cerevisiae* test for crossing over, the *S. pompe* test for forward mutation, and the V79 cell (HGPRT) test.

However, the rat hepatocyte DNA repair test does not appear to be valid (see below). Doses appear to be low: even if 50 ug/ml were cytotoxic as stated (and no data were provided to support that), dropping down to 5 ug/ml as the high dose does not seem justified. Furthermore, only 40 tiludronate-treated cells were read vs the 150 recommended. High doses in the yeast cell assays and V79 cells were set by "solubility limitations" or cytotoxicity, but no data were available to substantiate either claim.

RECOMMENDATIONS: Pharmacology recommends approval of tiludronate at 400 mg/day for 3 months to treat Paget's disease on the assumption that the clinical data supports this indication.

However, there are concerns about long-term use because of the narrow margin of safety in terms of bone quality in the three species examined (rats, dogs, monkeys).

Rats: In a 6-month study in rats, findings at 200 mg/kg (equivalent to 4x the human exposure on mg/m² basis) included irregular cartilage and decreased cortical mineralization in the femur.

Dogs: Ovariectomized dogs had reduced trabecular bone volume and connectivity as well as a decrease in osteoid zones with active osteoblasts. At the high dose (equivalent to 1x the human exposure on mg/m² basis), osteoblasts were inactive.

Baboons: In a 12-month study, findings included spontaneous rupture of the distal metaphysis at sampling along with total inhibition of spongiosa remodeling. In a 6-month baboon study at a higher dose, bone problems included: reduction of mineralization, signs of osteomalacia, and microfractures that suggested to the sponsor that "this diphosphonate has a toxic effect on osteoblasts at this dose" (4- to 5-fold the human C_{max}).

18 pages

PURGED

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020707

CHEMISTRY REVIEWS

DIVISION OF Metabolism and Endocrine DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-707 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 12-9-96

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
NDA (Original)	2-28-96	2-29-96	3-1-96
Amendments:	6-7-96	6-10-96	
	6-18-96	6-19-96	
	6-24-96	6-26-96	
(EA amendment)	10-28-96	10-29-96	
(Stability update)	10-28-96	10-29-96	
	11-21-96	11-22-96	

NAME & ADDRESS OF APPLICANT:

Sanofi Winthrop, Inc.
 9 Great Valley Parkway
 P.O. Box 3026
 Malvern, PA 19355

DRUG PRODUCT NAME:

Proprietary: Skelid (Tablets)
Nonproprietary: Tiludronate disodium (tablets)
Code Name/#: SR 41319B
Chem. type/Ther. Class: 1 S

PHARMACOL. CATEGORY/INDICATION:

Treatment of Paget's disease

DOSAGE FORM: Tablets (Oral)

STRENGTH: 200 mg tablets

ROUTE OF ADMINISTRATION: Oral

DISPENSED: X Rx OTC

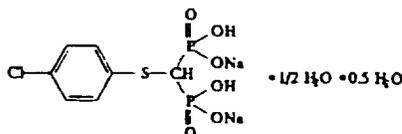
CHEMICAL NAMES, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

[[[p-chlorophenyl)thio] methylene] bis[phosphonic acid], disodium salt hydrated hemihydrate (IUPAC), [[[(p-chlorophenyl)thio] methylene] diphosphonic acid, disodium salt hydrated hemihydrate (INN).

Molecular weight: 362.6 (anhydrous form)

380.6 (hydrated hemihydrate form)

C₇H₄ClNa₂O₆P₂S (anhydrous) C₇H₄ClNa₂O₆P₂S.1/2H₂O.0.5H₂O (hemihydrate)



Hydrated Hemihydrate Form
 CAS Structure

SUPPORTING DOCUMENTS:**RELATED DOCUMENTS** : None**CONSULTS:** Environmental Assessment (HFD 004)**REMARKS/COMMENTS:**

In addition to this review, DMF for the drug substance, has been evaluated; and the related deficiencies are found in the draft letter of Review # 1 for this DMF.

The amendments of 6-7-96 and 10-28-96 provide updated Environmental Assessment information.

The amendment of 6-18-96 provides updated stability data for Skelid (Tablets). The amendment also corrects several minor typographical errors present in Vol. 1.2 of the NDA. The amendment of 10-28-96 provides still further updated stability information for the drug product.

The amendment of 11-21-96 provides updated stability data for the drug substance (tiludronate disodium).

Executed and unexecuted batch records were provided for the drug product used in the clinical trials, in the amendment dated 6-24-96.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry point of view, this submission is approvable pending satisfactory response to the chemistry deficiencies. The EA review and the review by the Division of Clinical Pharmacology and Biopharmaceutics are still pending. The EER was found acceptable as of 5-28-96.

cc:

Orig. NDA 20-707

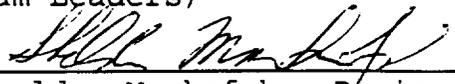
HFD-510/Division File

HFD-510/Sheldon Markofsky/12-9-96

HFD-510/R. Hedin (CSO)

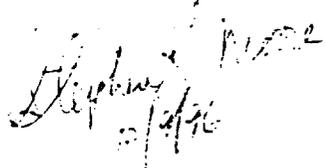
HFD-510/S. Moore/D-G Wu (Team Leaders)

HFD-510/J. Gibbs

 12-9-96
Sheldon Markofsky, Review Chemist

R/D Init by: Team Leader

filename: n20707h.wpd



JAN 21 1997

1

DIVISION OF Metabolism and Endocrine DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-707 **CHEM. REVIEW #:** 2 **REVIEW DATE:** 1-21-97

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE

Amendment: 12-4-96 12-6-96
Amendment: 12-31-96 1-7-97
Amendment: 1-10-97 1-14-97

NAME & ADDRESS OF APPLICANT:

Sanofi Winthrop, Inc.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

DRUG PRODUCT NAME:

Proprietary: Skelid (Tablets)
Nonproprietary: Tiludronate disodium (tablets)
Code Name/#: SR 41319B
Chem. type/Ther. Class: 1 S

PHARMACOL. CATEGORY/INDICATION:

Treatment of Paget's disease

DOSAGE FORM: Tablets (Oral)

STRENGTH: 200 mg tablets

ROUTE OF ADMINISTRATION: Oral

DISPENSED: X Rx OTC

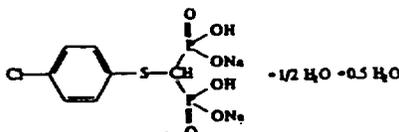
CHEMICAL NAMES, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

[[[p-chlorophenyl)thio] methylene] bis[phosphonic acid], disodium salt hydrated hemihydrate (IUPAC), [[[(p-chlorophenyl)thio] methylene] diphosphonic acid, disodium salt hydrated hemihydrate (INN).

Molecular weight: 362.6 (anhydrous form)

380.6 (hydrated hemihydrate form)

C₇H₇ClNa₂O₆P₂S (anhydrous) C₇H₇ClNa₂O₆P₂S.1/2H₂O.0.5H₂O (hemihydrate)



Hydrated Hemihydrate Form
CAS Structure

SUPPORTING DOCUMENTS:**RELATED DOCUMENTS** : None**CONSULTS:** Environmental Assessment (HFD 004)**REMARKS/COMMENTS:**

The amendment of 12-4-96 provides changes in the Environmental Assessment as requested by Philip Vincent of HFD-004. The amendments of 12-31-96 and 1-10-97 are responses to the comments and requests for information from Chemistry Review # 1 and Review #/ of DMF which were sent to the applicant by R. Hedin (CSO) in a facsimile communication, dated 12-12-96. The applicant has indicated that the DMF responses will be submitted as an amendment to the DMF file.

12/21/97
 R. Hedin

The firm has made the following phase 4 commitments.

CONCLUSIONS & RECOMMENDATIONS:

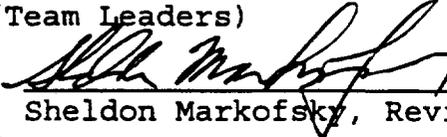
Satisfactory CMC information has been provided; and the application is approvable, from a Chemistry point of view.

The Environmental assessment documentation was found to be satisfactory, and a FONSI has been prepared (see EA review and FONSI, dated 12-5-96).

CSO: The applicant should be requested to correct the typographical errors in the storage statements of the HOW SUPPLIED section of the package insert and on the back panel of the cartons to read: 59-86°F [not 59-86°C].

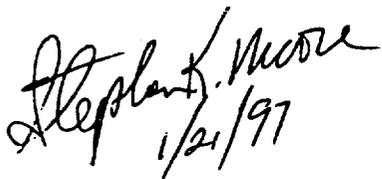
cc:

Orig. NDA 20-707
 HFD-510/Division File
 HFD-510/Sheldon Markofsky/1-21-97
 HFD-510/R. Hedin(CSO)
 HFD-510/S. Moore/D-G Wu (Team Leaders)
 HFD-510/J. Gibbs

 1-21-97
 Sheldon Markofsky, Review Chemist

R/D Init by: Team Leader

filename: n20707.2a

 1/21/97

656

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring , Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Metabolism and Endocrine D. P./ HFD-510
Attention: Sheldon Markofsky Phone: (301) 443-3520

Date: 8-20-96

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Skelid (Tablets) **NDA #:** 20-707

Company Name: Sanofi Winthrop, Inc.

Established name, including dosage form: Tiludronate disodium (Tablets) [oral]

Other trademarks by the same firm for companion products: None

Indications for Use (may be a summary if proposed statement is lengthy):
Treatment of Paget's disease

Initial comments from the submitter (concerns, observations, etc.):
Please indicate whether the name "Skelid" has been previously approved by the Labeling and Nomenclature Committee for this drug product. If the name has not been previously submitted please assess the proposed name.

filename: n20707t

NOTE: *Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.*

Rev. December 95

Consult #656 (HFD-510)

SKELID

tiludronate disodium tablets

The Committee found two look-alike/sound-alike conflicts with the proposed name: SKELAXIN and TICLID. However, the LNC feels there is a low potential for confusion with the previously marketed names. There were no misleading or fanciful aspects noted.

The LNC has no reason to find the proposed name unacceptable.

D. U. Boring 10/1/96 Chair
CDER Labeling and Nomenclature Committee

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 020707

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

**ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT**

FOR

SKELID®

(tiludronate disodium)

Oral Tablets 200 mg

NDA 20-707

**Division of Metabolic and Endocrine Drug Products
(HFD-510)**

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

FINDING OF NO SIGNIFICANT IMPACT

SKELID®

(tiludronate disodium)

Oral Tablets 200 mg

NDA 20-707

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for SKELID®, Sanofi Winthrop, Inc. has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) in the Tier 0 format which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

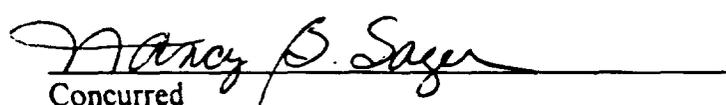
Tiludronate disodium is a chemically synthesized drug which is administered as a oral 200 mg tablet in the treatment of Paget's disease (osteitis deformans). The drug substance is manufactured by Sanofi Chimie, Aramon, France. The drug product manufacturer is Sanofi Winthrop, Ambares, France. The firms have provided a certification that the manufacturing facilities are: in compliance with all local and national environmental laws; in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and that approval and the subsequent increase in production at the facilities are not expected to affect compliance with current emission requirements or compliance with environmental laws. The finished drug product will be used in hospitals, clinics and homes throughout the United States.

Tiludronate disodium may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The projected environmental introduction concentration from use is less than 1 ppb. Therefore, the applicant has submitted a tier 0 EA without format items 7, 8, 9, 10 and 11 in accordance with the *Guidance for Industry for the Assessment in Human Drug Applications and Supplements*.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or outdated drug product will be disposed by incineration according to applicable environmental regulations. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

12/05/96 
DATE Prepared by
Phillip G. Vincent, Ph.D
Environmental Scientist
Center for Drug Evaluation and Research

12/13/96 
DATE Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

<i>Chaetomium globosum</i>	>1000
<i>Penicillium cyclopium</i>	>1000
<i>Azotobacter vinelandii</i>	100-200

Algal Inhibition/Toxicity:

<i>Selenastrum capricornatum</i> 14 days EC ₅₀ :	36.6 ppm
<i>Microcystis aeruginosa</i> 21 days EC ₅₀ :	13.3 ppm

Acute Aquatic Toxicity:

<i>Daphnia magna</i> 24 hour EC ₅₀ :	562 ppm
<i>Daphnia magna</i> 48 hour EC ₅₀ :	320 ppm
<i>Daphnia magna</i> 48 hour NOEL:	247 ppm

Activated Sludge Test: EC₅₀ SR 41319B: >100 mg/l

13. DISPOSAL CONSIDERATIONS

Discharge, treatment or disposal are subject to federal, state and/or local laws. Consider chemical degradation to a less toxic substance or incinerate after dissolving in a compatible waste solvent after collection in an impervious waste container. Contaminated clean up materials and personal protective equipment should be double (e.g., double sealed bags), marked and disposed by incineration. Outer waste containers should be labeled or marked to indicate contents and hazards for safe handling and disposal. Burn in an incinerator operating under applicable regulatory requirements.

14. TRANSPORTATION INFORMATION

IATA Classification: Not regulated as a dangerous good.
DOT (USA shipping name and classification): Not regulated as a hazardous material.
DOT Reportable Quantity: Not assigned.

15. REGULATORY INFORMATION

OSHA chemical hazards (29 CFR 1910.1200): Not applicable.

EPA List of Toxic Chemicals (40 CFR Part 372): Not applicable.

16. OTHER INFORMATION

Hazard label for this substance should state:

"I-2, D-2, F-1, C-1; for research and development purposes only by trained personnel. Properties of this substance have not been thoroughly evaluated. This substance is moderately toxic; danger of very serious, irreversible effects through inhalation, contact with skin or eyes, and if swallowed."

This material safety data sheet is intended for personnel handling this material in research and development. This material is not intended for human therapeutic use in this form.

This information is furnished without warranty, representation or license of any kind, except that it is accurate to the best of Sanofi Winthrop, Inc.'s knowledge or obtained from sources believed to be accurate. Sanofi Winthrop, Inc. does not assume any legal responsibility for use or reliance upon same. Customers are encouraged to conduct their own tests. Before using any product, read the label.

GUIDE FOR SANOFI RESEARCH DIVISION HAZARD CODES

HEALTH HAZARDS:

I = Inhalation Hazards
D = Dermal Hazards

0 = Basically inert
1 = Low hazard - minor, reversible effects
2 = Moderate hazard - may be harmful
3 = Severe hazard - effects may be dangerous
4 = Extreme hazard - effects dangerous at very low level of exposure

CHEMICAL/PHYSICAL HAZARDS:

F = Fire and explosion hazard

F0 = Basically inert
F1 = Low hazard
F2 = Moderate hazard - combustible
F3 = Severe hazard - flammable, readily ignites
F4 = Extreme hazard - very flammable

C = Reactivity hazard

C0 = Basically inert
C1 = Low hazard
C2 = Moderate hazard - heat sensitive, decomposes when heated
C3 = Severe hazard - decomposes violently when heated
C4 = Extreme hazard - decomposes very violently when heated

Additional comments: Indicate special hazard consideration

U = Unknown

E = Eye Hazard

● Description of the Drug Product

USAN: Tiludronate disodium

CAS: Phosphonic acid, [({4-chlorophenyl}thio)methylene] bis-disodium salt
Phosphonic acid, [({4-chlorophenyl}thio)methylene] bis-disodium salt, hydrated hemihydrate

IUPAC: [(4 chlorophenyl)thio]methylene diphosphonic acid hemihydrate disodium salt

INN: [({4-Chorphenyl}thio) methylene]bis-phosphonic acid hemihydrate disodium salt

Synonyms: Disodium dihydrogen [({p-chlorophenyl}thio) methylene] diphosphonate

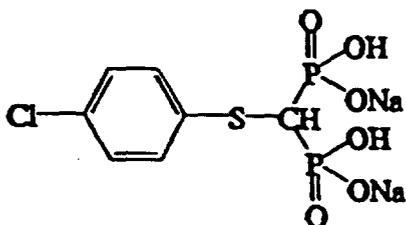
CAS Number: 149845-07-8 (anhydrous)
155453-10-4, 7732-18-5 (hydrated hemihydrate)

Internal code: SR41319B

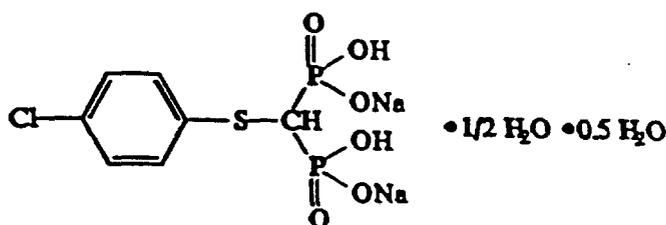
Molecular weight: 362.6 (anhydrous)
380.6 (hydrated hemihydrate of tiludronate disodium)

Empirical formula: $C_7H_7ClNa_2O_6P_2S \cdot \frac{1}{2} H_2O \cdot 0.5 H_2O$

Structural formula:



Anhydrous Form
USAN Structure



Hydrated Hemihydrate Form
CAS Structure

Physical chemical data:

Bulk Density: about 0.3 to 0.6 g/ml

Relative Density : 1.92 g/ml

Melting Point: 220-260°C

Vapor pressure at 40°C: 5×10^{-6} Pascals

Solubility in water: about 136-138 g/l

Solubility in alcohol: 0.1 g/l

Partition coefficient octanol/water: $\log K_{ow} < -3.8$

UV visible absorption: 263.5nm (buffer pH=4.8)

266nm (buffer pH=9)

Dissociation constant: 10.85 (pK1); 6.90 (pK2); 2.95 (pK3); 1.30 (pK4)

Health & safety:

Sanofi Health Protection Guideline (SHPG): 0.33 mg/m³ (TWA)

Dust explosion minimum ignition energy: > 500 mJ

Thermal stability: > 400°C

Toxicity: LD₅₀ Oral rat: 430 to 700 mg/kg

LD₅₀ Oral mouse: 1200 to 1400 mg/kg

3.4.6 Introduction of Substances into the Environment

The production of tiludronate disodium drug substance and drug product will utilize the same facilities currently being used for the production of other pharmaceutical products. For this assessment, engineering estimates are used to predict anticipated discharge levels; however, the evaluations do not reflect changes in treatment process or technology that might be implemented before actual approval of the tiludronate disodium.

Tiludronate disodium drug substance will be produced at Aramon, France. Tiludronate disodium (SKELID) drug product (tablets) will be produced at Ambares, France. The following evaluations of the anticipated environmental impact of tiludronate disodium drug substance is based on total fifth year projected production of tiludronate disodium and on existing environmental control systems at the production facilities.

- **Introduction from Production of Drug Substance at Aramon**

1. **Synthetic Route and Descriptive Summary: Confidential**

2. **Emissions from the Manufacturing Cycle**

The operations are conducted according to the written instructions of the master record, and throughout the operations, the operating parameters are checked at regular intervals and noted on the batch records.

The potential emissions to the environment include the drug substance and the constituents handled in the synthesis of tiludronate disodium and intermediates.

Constituents handled in the synthesis of tiludronate disodium and intermediates:

Drug substance: Tiludronate disodium (SR41319B)

Other materials: *Confidential*

3. Control In Place

A. Emissions From Process Operations

- Air Emissions

The facilities and equipment are designed to minimize air emissions to the environment and employee exposure to hazardous dust, fumes and vapors, through engineering, work practices and administrative controls.

- Emissions to the Aquatic Compartment

The wastewaters from manufacturing operations are pumped to an on-site treatment facility in compliance with the applicable permit limitations.

- Emissions to Terrestrial Compartment

No emission to the terrestrial compartment is expected.

B. Emissions From Storage of Chemical Substances

These materials are stored in secondary containment dikes so that in the event of a leak or failure of a container or a tank, the spillage is contained.

C. Emissions From Storage of Wastes

Solid wastes are stored in closed drums. Unrecoverable solvents are transferred through a closed system to portable or bulk storage tanks inerted with nitrogen. These materials are stored in secondary containment dikes special so that in the event of a leak or failure of a container tank, the spillage is contained.

Wastes are transported off site by licensed haulers to be incinerated by an approved plant.

D. Impurities

The impurities from the manufacturing cycle are not present in environmentally significant levels.

E. Occupational Safety and Health

Personnel in chemical production facilities are provided with appropriate personal protective equipment such as safety glasses, safety shoes, protective gloves/clothing and respiratory protection.

Employees are trained in proper operation of equipment to minimize potential safety, health or environmental risks and in emergency situations. Monitoring of exposure to hazardous materials is routinely conducted. Material Safety Data Sheets are available on-site for all the chemicals handled in the plant.

4. Manufacturing Process: Confidential

5. Compliance with Regulations

A. Statement of Compliance

Sanofi Chimie, Aramon, France will operate within its permit conditions during the production of tiludronate disodium.

● Introduction from Production of Drug Product at Ambares

1. Formulation Process

The product formulating process includes receiving, storage, sampling, weighing, granulation, compression, packaging and shipping of the drug product.

The following is a list of the chemicals, commercial products and wastes associated with the formulation of the drug product:

Formulation Constituents: Tiludronate disodium SR41319B
Other materials: *Confidential*

Nonhazardous Wastes:

Shipping containers

Packaging

Out-of-specification SKELID which cannot be reprocessed

Described below, for the three primary ecosystems (atmospheric, aquatic and terrestrial), are the potential emissions for the production of the drug product and their predicted impact on compliance with environmental and occupational health and safety regulations and permits.

2. Emissions from Formulation Operation

A. Air Emissions

Potential emissions are particulate (dust) from the weighing, sampling, granulation (associated with the mixing, drying and calibrating operations) and compression phases. Emissions will be controlled by dust collectors.

B. Aquatic Compartment

During the granulation phase, aqueous streams containing residual amounts of material are released into the residual water during the cleaning operations. This stream is collected and released in the collective purification system prior to discharge to the Ambares Municipal Wastewater Treatment Plant.

C. Waste

Solid waste is comprised of the following:

- Packaging
- Clean packaging

3. Compliance with Regulations

A. Occupational Safety and Health Compliance

Occupational Safety and Health Policy is managed in compliance with all applicable regulations. The formulating and packaging operations are frequently monitored by the authorities in charge of health, safety programs to demonstrate compliance with administrative policies, laws and application decrees.

Personnel in formulation and packaging facilities are provided with appropriate personal protective equipment such as safety glasses, safety shoes, protective gloves/clothing and respiratory protection. Employees are trained in proper operation of equipment to minimize potential safety, health or environmental risks and in emergency situations. Monitoring of exposure to hazardous materials is routinely conducted. Material Safety Data Sheets are available on-site for all the chemicals handled in the plant.

Out-of-specification tiludronate disodium product and formulating process related wastes are minimal hazards to human health. The drug product is stored in closed containers and packages using enclosed systems. Recommendations contained in the MSDS's will be adhered to for the safe handling of all constituent contaminated non-hazardous waste generated during the formulation of the drug product.

B. Statement of Compliance

Sanofi Winthrop, Ambares, France will operate within its permit conditions during the production of tiludronate disodium.

● **Emissions from Use**

Distribution of the drug product will be undertaken from the Sanofi Pharma distribution center, France to the Sanofi Winthrop, Inc. main distribution center in Des Plaines, Illinois where distribution to the United States will then occur.

Under the Sanofi Winthrop, Inc. Guaranteed Sales program, out-of-specification, unused or outdated drug product may be returned to the Des Plaines, Illinois facility for disposal. Quantities returned to the Des Plaines facility will be disposed of via the municipal waste treatment systems in accordance with environmental regulations.

The Des Plaines facility is a hazardous waste generator, EPA ID Number ILD 001870179. All hazardous waste is transported to a permitted incineration facility and incinerated.

Returned goods are treated to a product reclamation process. During the reclamation process, the drug product is removed from the packaging and the packaging is disposed of in an approved, off-site municipal solid waste landfill.

The drug product will be distributed to clinics and pharmacies throughout the United States and its territories. The primary route of entry into the environment is projected to be via human excretions.

Metabolism studies indicate there is no significant evidence of drug product transformation in human male subjects and rats. This would indicate that the drug product will enter into Publicly Owned Treatment Works (POTW) in an unmetabolized form. The low vapor pressure and high water solubility characteristics for the drug substance indicate unmetabolized drug substance will remain in the water compartment with no migration to the atmospheric compartment. A calculation of the Maximum Expected Emitted Concentration (MEEC) to the aquatic compartment per the CDER Guidance for Industry for the Submission

of an Environmental Assessment in Human Drug Applications and Supplements, November 1995 (CDER EA Guidance Document) indicates an environmental concentration of less than one part per billion (ppb).

- **Emissions from Disposal**

Since wastes from pharmaceutical production and distribution are disposed at incineration and landfill facilities regulated by the EPA or State agencies which consider environmental impacts from waste disposal, the Expected Introduction Concentration (EIC) does not need to be calculated.

3.4.7-11 Environmental Fate and Effects of the Substances Introduced into the Environment Use of Energy and Resources, Mitigation Measures, and Alternatives to the Proposed Action

Pursuant to 21 CFR 25.31a(a) and CDER EA Guidance Document, EA format items 7, 8, 9, 10, and 11 are not necessary for drugs which enter the environment (MEEC) at less than a one part per billion (ppb) "Tier 0" concentration.

3.4.12 List of Contributors and Preparers

- **List of Contributors**

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Sanofi Winthrop, Inc.
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3.4.13 Certification

The undersigned certified that the information presented is true, accurate and complete to the best knowledge of the department responsible for the preparation of the environmental assessment.

George J. Pointet For MARCEL Pointet
Marcel Pointet
Director, Environmental Affairs
Sanofi Chimie

Dec 4, 1996
Date

3.4.14 References

Data presented in the previous pages were obtained from the following sources:

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27. Inveresk Research International Limited, Final Report #10409, "Determination of the Minimum Inhibition Concentration for SR41319B", October 24, 1994.
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primarily with warehousing operations with light industrial sites located to the north, west and south with residential areas to the east.

The climate is temperate with an annual mean temperature of 49EF and an annual mean precipitation of 33 inches. Prevalent winds are from the west with an average wind speed of 10.3 miles per hour.

2. Description of Operations at the Facility

The site contains an 86,000 square foot warehousing and distribution center and is the primary distribution facility for Sanofi Winthrop pharmaceutical products to customers, primarily wholesale and hospital accounts both domestically and internationally. The site also serves as the nationwide center for return of outdated, out-of-specification or unused products. There are no manufacturing operations located on the site.

3. Applicable Environmental Regulations

Sanofi Winthrop Incorporated - Des Plaines facility is a hazardous waste generator. During the current contract period, all industrial hazardous waste is transported via JB Hunt Special Commodities, to ENSCO, American Oil Road, El Dorado, AK 71730 for incineration. Non-hazardous waste is brokered to incineration facilities, currently OGDEN Martin of Lake, Florida with an option to use ENSCO and Chambers Medical Technologies of South Carolina, Inc.

1. Hazardous Waste EPA ID Number: ILD 001870179
2. Waste Transport: JB Hunt Special Commodities: EPA ID Number ARD 981908551
3. Disposal Facilities: ENSCO, Inc.: EPA ID Number ARD 069748192

As the facility is a Distribution Center **ONLY**, there are no processes at Des Plaines, and therefore, industrial non-hazardous solid wastes are not disposed at local landfill sites, nor are there any wastewater or air emission permit regulations.

● Location Where the Product Will Be Used

The drug product is intended for the use in and will be distributed to the hospitals, private doctors offices and pharmacies throughout the United States.

● **Locations Where the Product Will Be Disposed**

Under the Sanofi Winthrop, Inc. Guaranteed Sales program, out-of-specification, unused or outdated drug product may be returned to the Des Plaines, Illinois facility for disposal. Quantities returned to the Des Plaines facility will be shipped to licensed facilities for disposal by incineration according to applicable environmental regulations. Hospitals and offices may also dispose of the drug product as part of their medical waste stream.

3.4.5 Identification of Chemical Substances that are the Subject of the Proposed Action

● Description of the Drug Substance

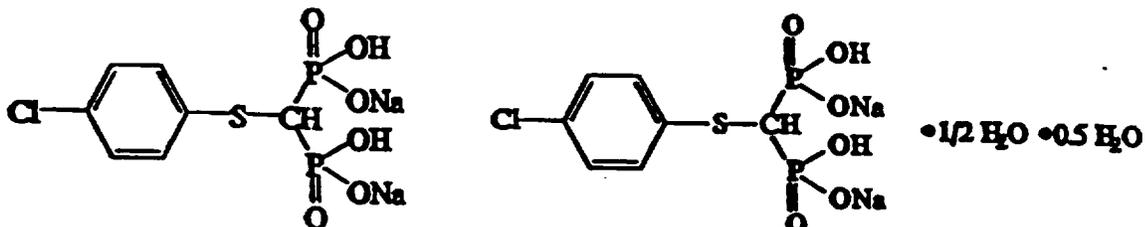
USAN:	Tiludronate disodium
CAS:	Phosphonic acid,[[[(4-chlorophenyl)thio]methylene] bis-, disodium salt
CAS:	Phosphonic acid,[[[(4-chlorophenyl)thio]methylene] bis-, disodium salt, hydrated hemihydrate*
IUPAC:	[[[(4-Chlorophenyl)thio] methylene] bis[phosphonic acid], disodium salt hydrated hemihydrate*
INN:	[[[(p-chlorophenyl)thio] methylene] diphosphonic acid, disodium salt hydrated hemihydrate*
Synonyms:	Disodium dihydrogen [[[(p-chlorophenyl)thio] methylene] diphosphonate; disodium tiludronate
CAS Number:	149845-07-8 (anhydrous) 155453-10-4, 7732-18-5 ¹ (hydrated hemihydrate)*
Internal code:	SR41319B
Molecular weight:	362.6 (anhydrous tiludronate disodium) 380.6 (hydrated hemihydrate tiludronate disodium) ²
Empirical formula:	C ₇ H ₇ ClNa ₂ O ₆ P ₂ S (anhydrous form) C ₇ H ₇ ClNa ₂ O ₆ P ₂ S•½H ₂ O•0.5H ₂ O (hydrated hemihydrate form)
Physical description:	White to off-white powder

*Tiludronate disodium is synthesized as the hydrated hemihydrate

¹ The hydrated hemihydrate of the form of tiludronate disodium is represented by two CAS registry numbers. The 155453-10-4 represents the originally registered hemihydrate structure which was subsequently revised to the currently registered hydrated hemihydrate structure represented by 155453-10-4, 7732-18-5.

² This is a revised CAS structure. The original CAS structure was the hemihydrate form with a molecular weight of 371.6 indicating only one ½ mole of water of crystallization. Several earlier reports may refer to this original hemihydrate form instead of the current hydrate hemihydrate form containing two ½ moles of water.

Structural formula:



Anhydrous Form
USAN Structure

Hydrated Hemihydrate Form
CAS Structure

Physical chemical data:

Bulk Density: about 0.3 to 0.6 g/ml

Density: 1.92 g/ml

Melting Point: 220-260°C

Vapor pressure at 40°C: $<5 \times 10^{-6}$ Pascals

Solubility in water: about 136-138 g/l

Solubility in alcohol: <0.1 g/l

Partition coefficient octanol/water: $\log K_{ow} < -3.8$

UV visible absorption: 264 nm (buffer pH=4.8); 266 nm (buffer pH=9)

Dissociation constant: 10.85 (pK1); 6.90 (pK2); 2.95 (pK3); 1.30 (pK4)

Health & safety:

Sanofi Health Protection Guideline (SHPG): 0.33 mg/m³ (TWA)

Dust explosion minimum ignition energy: >500 mJ

Thermal stability: $>400^\circ\text{C}$

Toxicity:

LD₅₀ Oral rat: 430 to 700 mg/kg

LD₅₀ Oral mouse: 1200 to 1400 mg/kg



MATERIAL SAFETY DATA SHEET

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Sanofi Winthrop, Inc.
Sanofi Research Division
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

For Emergency Information, call (610) 889-8911
For Technical Information, call (610) 889-8687

Approval Date: October 23, 1996

Substance Name: Tiludronate disodium

Chemical Name: [{"(4-chlorophenyl)thio}methylene] bis(phosphoric acid), disodium salt hydrated hemihydrate

Synonyms: SR 41319B, tiludronic acid (di)sodium, disodium tiludronate, Skelid

Intended Use: Long-term oral dose therapy of Paget's disease of bone and post-menopausal osteoporosis.

For use within Sanofi Research Division. Prior approval by Health, Safety and Environmental Affairs is required for distribution of this MSDS to anyone other than a Sanofi Research Division employee.

2. COMPOSITION / INFORMATION ON INGREDIENTS:

<u>Component(s)</u>	<u>Weight %</u>	<u>CAS #</u>	<u>SR#</u>	<u>Exposure Guideline</u>
Tiludronate disodium	100	149845-07-8 (anhydrous) 155453-10-4, 7732-18-5 (hydrated hemihydrate)	SR 41319B	0.33mg/m ³

3. HAZARD IDENTIFICATION:

Hazard Codes: (see description last page)

I:2 D:2 F:1 C:1

Hazard Summary:

Health:

Chemical/Physical

combustible

4. FIRST AID MEASURES

Signs and Symptoms:

Inhalation: Remove to fresh air. If person is not breathing, give artificial respiration. If breathing is difficult, administer oxygen. Seek medical attention immediately.

Eyes: Flush with water for at least 15 minutes. Seek medical attention immediately.

Skin: Flush area with large amounts of water for 15 minutes while removing contaminated clothing. Use soap if available. Seek medical attention immediately.

Ingestion: Consume large amounts of water. Never give anything by mouth to an unconscious person. Seek medical attention immediately.

Note to Physician: Not determined.

5. FIRE AND EXPLOSION PROPERTIES / FIRE FIGHTING MEASURES

Prevention of Fire and Explosion:

Minimize dust generation and accumulation. Keep away from heat, sparks and open flame. Refer to NFPA 654, "Prevention of Fire and Dust Explosions in the Chemical, Dye, Pharmaceutical and Plastics Industries."

A. Dust Explosion Risk:

A/B Classification: Group A (flammable)

Combustibility tests indicate the material burned producing a very large orange flame with no pressure evident.

Minimum Ignition Energy (MIE): 500mj

Take adequate precautions; finely divided solid materials (dusts and fines), when dispersed in the air, can fuel particularly violent and destructive explosions. This material presents an electrostatic discharge hazard.

B. Thermal Stability: Not determined.

C. Electrostatic Risk: Not determined.

D. Special Fire-Fighting Procedures: Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes. Use water spray to keep fire exposed containers cool.

Hazardous Combustion Products: May contain oxides of carbon, sulfur and hydrogen chloride.

Means of Extinction: Water spray, carbon dioxide or dry chemical

6. ACCIDENTAL RELEASE MEASURES

Prevention:

To minimize hazards from accidental breakage of containers, substance should be transported or stored within secondary containers, pans or trays to contain spillage and simplify cleanup. Use protective coatings and/or barrier sheeting in use areas where possibility of spillage exists to simplify cleanup.

Response:

If a small spill occurs, wipe up spill with moistened cloth and place in an impervious container. Wash the contaminated area with a suitable solvent or water plus a surfactant if necessary. Place waste container inside an outer container and remove from the isolator or safety cabinet to a labeled container marked for disposal (see section 13).

During a large spill/release emergency, evacuate non-essential personnel from the area. Wear protective equipment to prevent inhalation or eye/skin contact [see section 8]. Minimize dust generation by using a HEPA filter vacuum to clean spillage. If not available, use water/dilute solution of surfactant to dampen the spilled substance before collecting. Gently scoop up and place into suitable impervious container for disposal [see section 13]. Wash spillage area with surfactant and water. Remove any contaminated clothing, personal protective equipment and barrier sheeting, and place in a double sealed waste container.

7. HANDLING AND STORAGE PRECAUTIONS

Only Authorized and Trained Personnel Shall Handle This Compound.

Keep container closed and protect from contamination. Store in a cool, dry place. Store and transport within secondary containers, pans or trays.

Do not breathe airborne substance, and do not allow contact with eyes, skin or clothing. Use only with containment or isolation facilities and equipment, personal protective equipment and safe work practices. Wash thoroughly after handling [see section 8].

Label all containers with hazard information.

8. SPECIAL PROTECTIVE MEASURES

A. **Exposure Limits:** The substance is expected to be a moderate toxic hazard. Sanofi Exposure Guideline: 0.33mg/m³.

B. **Preventive Measures:** Restrict access to the work area and take precautions to contain material within restricted area. Implement appropriate work practices and procedures to eliminate exposure.

Small quantities may be handled on the open bench only if there is no potential for generating airborne contaminants. Otherwise, containment (e.g., fumehood) must be used. Wear safety glasses, gloves and a laboratory coat.

Large quantities where there is a high potential for generating airborne contaminants must be handled in containment. If containment is not practical then facility controls and personal protective measures (e.g., gloves taped to disposable Tyvek™ suits, air supplied suit) may be necessary.

For operations requiring prolonged or repeated handling, double gloves and skin cover should be worn. Work only in accordance with chemical hygiene plans and instructions for safe handling during both normal and emergency operations. Wash thoroughly immediately after use. Contain and control the emissions from experiments, and properly dispose of wastes generated.

- C. **Ventilation:** Use contained process enclosures, local exhaust ventilation or other engineering controls to maintain aerosols below the exposure limit. All operations must be performed in rooms with negative ventilation.
- D. **Respiratory Protection:** If engineering controls cannot maintain airborne concentrations below exposure limits respirators should be worn. Respiratory protection must be in compliance with the OSHA Respiratory Protection Standard, 29 CFR 1910.134.
- E. **Eye Protection:** Special protection is required to protect employees from exposure to dusts, mists, aerosols, splashes and contact. Wear safety glasses with side shields, a full-face shield or full-face respirator as appropriate.
- F. **Hand Protection:** Wear impervious chemical resistant gloves (e.g. nitrile). Clean gloves inside the containment device to prevent lab contamination. Double gloves should be used when in contact with drug substance.
- G. **Recommended Decontamination Facilities:** An eye wash, safety shower and washing facilities shall be available in the immediate area.
- H. **Medical Conditions Aggravated:** May aggravate renal disorders, gastric disorders or hypoparathyroidism. Abnormal responders may also include those taking NSAIDS.

9. PHYSICAL AND CHEMICAL PROPERTIES

Molecular Formula: $C_7H_7ClNa_2O_6SP_2S$ (anhydrous form)
 $C_7H_7ClNa_2O_6SP_2S \cdot 1/2H_2O \cdot 0.5H_2O$ (hydrated hemihydrate)

Molecular Weight: 362.6 (anhydrous)
380.6 (hydrated hemihydrate)

Physical Description: White to off white crystalline powder

Melting Point (°C): 220 - 260

Vapor Pressure (Pascal): $<5 \times 10^{-6}$ at 40°C

Solubility in Water (@ 20 °C): About 136 - 138 g/L (very soluble)

Partition Coefficient (octanol/water): $\log K_{ow} = -3.8$ (low, not expected to absorb into soil compartment)

Bulk Density (g/cm³): 0.4 to 0.6

Dissociation Constant (pK): 10.85(pk₁), 6.90(pk₂), 2.95(pk₃), 1.30(pk₄)

Hydrolysis Rate (t_{1/2}): Essentially stable

UV/Visible absorption (nm): 263 (Lambda max 0.04 M Acetate/0.2 M NaCl pH 4.8)
266 (Lambda max 0.04 M Borate/0.2 M NaCl pH 9.0)

Soil sorption/desorption (K): 104-363 (Non-mobile compound in soil)

(K_{ow}): 11544-24227
(K_{ow}): 6494-13977

10. STABILITY AND REACTIVITY

Thermal Stability: See section 5.

Incompatibility: Incompatibility of this material has not been investigated. As a precautionary measure, keep away from ignition sources including electrostatic charge, heat, sparks and flame. Keep from contact with oxidizing materials, highly oxygenated or halogenated solvents and organic compounds containing reducible functional groups.

11. TOXICOLOGICAL PROPERTIES

Toxicological properties have not been thoroughly investigated. Unless otherwise stated, a suspension containing tiludronate drug substance was tested.

- A. **Effects of Acute Exposure:** Following single dose administration pharmacological effects associated with altered bone turnover (decreased serum alkaline phosphatase and excretion of hydroxyproline in urine) may be observed. Adverse effects observed in healthy male volunteers include elevation of serum creatinine concentration, changes in brush border enzymes and protein resorption (suggestive of a proximal tubule reaction) in healthy male volunteers.

Dust from tablets is expected to be a moderate toxic hazard following inhalation, ingestion, skin or eye exposure. Based on irritancy studies in the rabbit, dust is expected to be a slight skin irritant and moderate eye irritant.

Toxicity Data:

<u>Route</u>	<u>Test</u>	<u>Species</u>	<u>Results</u>
Oral	LD ₅₀	rat	430-700 mg/kg
		mouse	1200-1400 mg/kg
Intravenous(solution)	LD ₅₀	rat	120-175 mg/kg
		mouse	120-175 mg/kg

- B. **Effects of Chronic (Repeated) Exposure:** Pharmacological effects associated with altered bone turnover include decreased serum alkaline phosphatase and urinary hydroxyproline. Gastrointestinal effects (abdominal pain, loss of appetite, nausea and diarrhea) are the most frequently reported adverse events following repeated administration in the clinic. The incidence of these events are dose related. Dose related renal effects (proximal tubulopathy, discoloration, interstitial tubulonephritis) have been observed in the mouse, rat, dog and baboon. Elevated serum creatine levels and/or BUN and acute renal insufficiency have been observed in the clinic. Severe transient hepatitis, a severe skin reaction, a slight reversible decrease in lymphocyte subpopulations, and headaches have also been observed in patients receiving tiludronate in clinical trials.
- C. **Developmental Toxicity:** No developmental toxicity was observed in the animal studies conducted at doses which did not produce maternal toxicity.
- D. **Reproductive Toxicity:** No reproductive toxicity was observed in the animal studies conducted at doses which did not produce maternal toxicity.

E. Mutagenicity:

Toxicity Data:

<u>Test System</u>	<u>Results</u>
Ames (<i>S. typhimurium</i> / <i>E. Coli</i>) test	Negative (± S9 metabolizing system)
<i>In vivo</i> mouse micronucleus test	Negative
<i>In vitro</i> mammalian & non-mammalian cell systems	Negative
DNA repair assay (rat hepatocytes)	Negative
Chromosomal aberration assay (human lymphocytes)	Negative (± S9 metabolizing system)

F. Carcinogenicity:

Toxicity Data:

<u>Test</u>	<u>Species</u>	<u>Results</u>
Oral (1.5 years)	Mouse	Negative
Oral (2.0 years)	Rat	Negative

12. ECOLOGICAL INFORMATION

Summary: Tiludronate disodium is freely soluble in water with an octanol/water partition coefficient of $\text{Log } K_{ow} < -3.8$. This suggests the compound will migrate to the water compartment.

This product is very stable. The aerobic biodegradation is zero in 28 days, therefore the product is classified as not readily degradable. Tiludronate disodium has shown low to slight toxicity in microbial inhibition toxicity and activated sludge tests.

Oxygen Demand Data:

<u>5-day BOD</u>	
Reference	102 mg/l
1 mg/l	0 mg/l
10 mg/l	0 mg/l
100 mg/l	0 mg/l
1000 mg/l	0 mg/l

Chemical Oxygen Demand and Theoretical Oxygen Demand

COD	for SR 41319B = 0.825 mg O ₂ /mg
ThOD	for SR 41319B = 0.861 mg O ₂ /mg

Biodegradation: 28 Day BOD = 0% Biodegradation

Photodegradation: Buffered aqueous solution pH 7 = 4.2 hours
 Deionized water = 8.9 hours

Microbial Inhibition Toxicity:

<u>Micro-organism</u>	<u>Minimum Inhibitory Concentration (ppm)</u>
<i>Bacillus cereus</i>	>1000
<i>Nustoc muscorum</i>	800-1000

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3.4 ENVIRONMENTAL ASSESSMENT

- 3.4.1 Date** December 3, 1996
- 3.4.2 Name of Applicant** Sanofi Winthrop, Inc.
- 3.4.3 Address**

DMF Holder Sanofi Chimie
9 Rue Du President Allende
94256 Gentilly
France

Contact for FDA Sanofi Winthrop, Inc.
Drug Regulatory Affairs
90 Park Avenue
New York, NY 10178
USA

3.4.4 Description of the Proposed Action

- **Description of the Requested Approval**

Sanofi Winthrop, Inc. is requesting approval for use of SKELID tablets (tiludronate disodium) for the treatment of Paget's disease (osteitis deformans).

Tiludronate disodium as a novel bisphosphonate is characterized by the presence of a phosphorous-carbon-phosphorous (P-C-P) linkage. Bisphosphonates are analogues of pyrophosphate (P-O-P), an important component of bone believed to be a factor in the mineralization of bone matrix. The carbon-for-oxygen substitution renders bisphosphonates resistant to degradation by pyrophosphatases. Like other bisphosphonates, tiludronate disodium undergoes little, if any, metabolism with no metabolites identified.

- **Need for the Proposed Action**

Paget's disease is a chronic skeletal disorder that may result in enlarged and deformed bones in one or more regions of the body. This excessive rate of bone remodeling can result in bone that is dense but fragile. Tiludronate disodium provides a safe, effective treatment for Paget's disease.

● **Location Where Drug Substance Will Be Produced**

The applicant proposes to manufacture the drug substance at:

Sanofi Chimie
Route d'Avignon
30390 Aramon
France

1. Geographic Location and Description

The plant of Sanofi Chimie, Aramon, France is located about 2 miles (3 kilometers) north of Aramon, a town of about 3000 inhabitants.

The manufacturing site consists of approximately 50 acres with about 30 buildings housing manufacturing operations, quality control, warehouses, maintenance, process development laboratories and administrative and management offices.

2. Description of Operations at the Facility

The operations at the facility include manufacturing and warehousing of bulk intermediates and fine pharmaceutical chemicals. The Prefectoral Order No. 89-006N of January 30, 1989 authorizes Sanofi Chimie Aramon to handle chemical and pharmaceutical substances in the Aramon facility where the tiludronate disodium will be manufactured.

Waste management, minimization and spill prevention programs, policies and procedures have been instituted to ensure proper compliance with all site regulations. A waste water treatment facility receives all waste water from the plant. After treatment, the water is discharged to the Rhone River in accordance with established permit limitations.

3. Applicable Environmental Regulations

The chemical manufacturing activity is governed by:

Law No. 76-663 of July 19, 1976 relative to Classified Facilities for the Protection of the Environment (*loi No. 76-663 du 19 Juillet 1976 relative aux Installations Classées pour la Protection de l' Environnement*). Last modified by the law No. 93-3 of January 4, 1993.

Decree No. 77-1133 of September 21, 1977 then for the application of the Law No. 76-663 of July 19, 1976 relative to Classified Facilities for the Protection of the Environment. Last modified by the Decree No. 94-484 of January 9, 1994.

Application of the Laws and Decrees relative to the protection of the Environment is managed by the Ministry of the Environment and its technical agency the DRIRE (*Direction Regionale de l'Industrie, de la Recherche et de l'Environnement* - Regional Directorate of Industry, Research and the Environment), in connection with the Ministry of Agriculture, the Ministry of Development, the Ministry of Industry and the Ministry of Health.

The Prefect of the Region is the State representative. The Prefect is responsible, in the Region, for the application of all regulations. The Prefect is assisted for the protection of the Environment by the DRIRE, representative of the Ministry of the Environment.

The chemical manufacturing activity requires the Prefect to issue a Prefectoral Authorization Order and a statement of acceptance, if any modification to the previous authorized application is made. This official submission to the authorities must include:

- a complete description of the activities at the plant
- measures and processes implemented to reduce pollution
- an analysis of the impact of the industrial activities on the surrounding environment
- a technical and economic justification for the measures to be taken
- a statement about conformity of the facilities with legislative and regulatory rules on occupational health and safety

The Prefectoral Order No. 89-006N fixes rules of operation for the plant and in particular, applicable limits to protect the environment as a function of the sensitivity of the environment and in the application of legal measures including the following administrative polices, Laws and application Decrees:

- the Water Policy based on Law No. 92-3, January 3, 1992
- the Noise Policy, based on Law No. 92-1444, December 31, 1992
- the Policy concerning atmospheric pollution and smells, based on Law No. 61-842, August 2, 1961
- the Policy concerning elimination of waste and recovery of materials, based on Law No. 75-633, July 15, 1975
- the Fishing and Aquatic Environments Policy, in application of the Rural Code (Articles L230 to L239-1)
- The Town Planning Law, in application of the Town Planning Code

4. Certification

The Policy of Classified Facilities for Protection of the Environment is specially monitored by the DRIRE (*Direction Régionale de l'Industrie, de la Recherche et de l'Environnement* -

Regional Directorate of Industry, Research and the Environment) representative of the Ministry of Environment.

The DRIRE has submitted a letter certifying that the pollution control authorities reviewed the Sanofi Chimie plant of Aramon and stating the manufacturing process of the drug substance tiludronate disodium, is in compliance with applicable environmental and occupational safety regulations.

A letter is included (Figure 1) from the Director Establishment, Sanofi Chimie, Aramon, certifying that the plant is in compliance with all local and national environmental laws, in compliance with all emission requirements set forth in all permits, and that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

- **Location Where the Drug Product Will Be Produced**

The applicant proposes to formulate and package the drug product at:

Sanofi Winthrop Industrie
1 Rue De La Vierge
33440 Ambares
France

- 1. Geographic Location and Description**

The plant of Sanofi Winthrop Industrie, Ambares, France is located southeast of Ambares a town of about 10,000 inhabitants and about 12.4 miles (20 kilometers) east of Bordeaux.

The manufacturing site consists of approximately 32.5 acres with about 14 buildings. These buildings consist of house manufacturing operations, quality control, warehouses and maintenance operations.

- 2. Description of Operation at the Facility**

The operations at the facility include the preparation and packaging of pharmaceutical products for human use. The Prefectoral Order No. 13847 of July 21, 1995 authorizes Sanofi Winthrop Industrie Ambares to handle chemical and pharmaceutical substances in the Ambares facility where the tiludronate disodium will be manufactured.

Waste management, minimization and spill prevention programs, policies and procedures have been instituted to ensure proper compliance with all site regulations. A waste water collection system receives all waste water from the plant where it is monitored and discharged to the Ambares municipal wastewater treatment facility in accordance with established permit limitations.

USINE D'ARAMON
ROUTE D'AVIGNON
38390 ARAMON
TEL. : (33) 66 87 71 71
FAX : (33) 66 87 72 91
Téléc. 030 024



PEMR - 96/2157

SANOFI WINTHROP, Inc.
9, Great Valley Parkway
MALVERN, PA 19355
U.S.A.

Aramon, OCTOBER 25, 1996

Re : Drug Substance **TILUDRONATE DISODIUM**
Certification of Compliance
With Environmental Regulations

Dear Sirs,

Pursuant to U.S. Executive Order 12114 "Environmental Effects Abroad of Major Federal Actions", the undersigned official certifies that all Tiludronate Disodium manufacturing facilities named below are in compliance with, or on an enforceable schedule to be in compliance with all local and national environmental laws and all emission requirements set forth in all permits, and that approval and the subsequent increase in production at the facilities named below is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Sincerely yours,

Pierre CHASTAGNIER

Title : Plant Manager
Facilities : ARAMON Facilities
Date : October 25, 1996

SANOFI-CHIME - S.A. AU CAPITAL DE 66.815.000 F.
SIÈGE SOCIAL : 9, RUE DU PRÉSIDENT ALLENDE - 92256 GENÈVEY CEDEX
R.C.S. GENÈVE 6 992 032 874 - N° SIREN 992 032 874
N° SIRET 992 032 874 00139

EN 2 - Ref. 04117

Figure 1: Certification Letter from Aramon Facility

3. Applicable Environmental Regulations

The pharmaceutical formulation and packaging activities are governed by the same laws and decrees outlined in Section 3.4.4 (Applicable Environmental Regulations) on pages 2 and 3.

The law No. 76-663 of July 19, 1976 relating to the installations classified for protecting the environment (*loi No. 76-663 du 19 Juillet 1976 relative aux Installations Classees pour la Protection de l' Environnement*).

The Prefectoral Order No. 13847 fixes rules of operation for the plant and in particular, applicable limits to protect the environment as a function of the sensitivity of the environment and in the application of legal measures including the following administrative polices, Laws and application Decrees:

The order of the prefect No.7-430 of May 5, 1965 and the earlier orders having authorized the French company of LABAZ Laboratories to operate in AMBARES, along National Route 10, a pharmaceutical products laboratory.

The order of prefect No. 12467 of October 5, 1984 having authorized the "European Pharmaceutical Center" successor of LABAZ Laboratories to install within the Ambares facility a pharmaceutical and technical location and a liquid warehouse.

The order of the prefect No. 12688 of June 16, 1986 having set at the "European Pharmaceutical Center" additional prescriptions, considering the expansion of its warehouse of inflammable liquids and collection and regulatory changes in noise and industrial waste collection.

Order of the prefect No. 12893 of November 16, 1987 imposing at European Pharmaceutical Center additional technical measures due to an increase in the storage of inflammable liquids at the Ambares facility.

The dossier dated January 21, 1992, relating to changes in activity (industrial water network and inflammable liquid storage), produced by Sanofi Winthrop Industrie, a new name for the Sanofi Pharma Industrie (ex European Pharmaceutical Center), at the Ambares site.

The Prefect's Order No. 13994 of June 3, 1992 authorizes Sanofi Winthrop Industrie to carry out the modifications to the Ambares facility.

4. Certification

The DRIRE, French government agency responsible for administering environmental programs and policies has submitted a letter certifying that the pollution control authorities reviewed the Sanofi Winthrop plant of Ambares and stating the manufacturing process of the drug product SKELID, is in compliance with applicable environmental and occupational safety regulations.

A letter is included (Figure 2) from the Director Establishment, Sanofi Winthrop, Ambares, certifying that the plant is in compliance with all local and national environmental laws, in compliance with all emission requirements set forth in all permits, and that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

● **Location Where Drug Product Will Be Shipped**

The applicant proposes to ship the drug product from:

Sanofi Pharma, Inc.
5 Rue Des Bruyeres and 7 Rue Des Genets
Saint Loubes, FRANCE

1. Geographic Location and Description

The facility of Sanofi Pharma, Saint Loubes, France is located southwest of Saint Loubes, a town of about 5,800 inhabitants and about 31 miles (19 kilometer) east of Bordeaux.

The facility housing warehousing, administration and offices consists of two sites approximately 2.5 acres and 10 acres. The sites are approximately 3 mile apart.

2. Description of Operation at the Facility

The operations at the facility include the storage and repackaging of pharmaceutical products for human use. The Prefectoral Order No. 12970 of June 2, 1988 authorizes Sanofi Pharma, Saint Loubes to handle pharmaceutical substances in the Saint Loubes facility where the packaged SKELID will be stored and shipped.

Waste management, minimization and spill prevention programs, policies and procedures have been instituted to ensure proper compliance with all site regulations.

SANOFI
1, RUE DE LA VIERGE - 33440 AMBARES
TELEPHONE 67 77 36 00
TELECOPIEUR 67 77 36 00
SIRET: 778 642 267 00101
APE 244 C



JMG/NS-178

October 24, 1996

ATTESTATION

As the responsible company official at the SANOFI WINTHROP, Ambares Facility, I certify that the facility is in compliance with all local and national and environmental laws and emission requirements set forth in all permits.

I also certify that the subsequent increase in production to manufacture tildronate disodium (SKELID) at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Sincerely,

A handwritten signature in black ink, appearing to read "Jean-Marc GEORGES".

Jean-Marc GEORGES
Plant Manager

SA AN CAPITAL DE 54.000.000 F
SIRET: 778 642 267 00100 - APE 741 J
Régis Siret 61, Avenue Pasteur - 92500 - GENNEVILLIERS CEDIX

Figure 2: Certification from Ambares Facility

The wastewater from the plant is discharged to the Saint Loubes municipal wastewater treatment facility in accordance with established permit limitations.

3. Applicable Environmental Regulations

The pharmaceutical warehousing activities are governed by the same laws and decrees outlined in Section 3.4.4 (Applicable Environmental Regulations) on pages 2 and 3.

The Prefectoral Order No. 12970 fixes rules of operation for the plant and in particular, applicable limits to protect the environment as a function of the sensitivity of the environment and in the application of legal measures including the following administrative polices, Laws and application Decrees:

The order of the prefect No.76.663 on July 19, 1976 relating to the installation filed for protecting the environment.

The order of prefect No. 77.1133 on September 21, 1977 being authorized to be created in Saint Loubes in the industrial zone "La Lande", a warehouse and distribution center for pharmaceutical products.

4. Certification

The DRIRE, french government agency responsible for administering environmental programs and policies has submitted a letter certifying that the pollution control authorities reviewed the Sanofi Pharma facility of Saint Loubes and stating the warehousing of the packaged product SKELID, is in compliance with applicable environmental and occupational safety regulations.

● Location Where Drug Product Will Be Distributed

The applicant proposes to ship the drug product to and from:

Sanofi Winthrop L.P.
200 East Oakton Street
Des Plaines, IL 60017

1. Geographic Location and Description

The primary distribution center for Sanofi Winthrop, Inc. is located on approximately seven acres in the city of Des Plaines in Northwest Cook County, Illinois. The site is surrounded

primarily with warehousing operations with light industrial sites located to the north, west and south with residential areas to the east.

The climate is temperate with an annual mean temperature of 49°F and an annual mean precipitation of 33 inches. Prevalent winds are from the west with an average wind speed of 10.3 miles per hour.

2. Description of Operations at the Facility

The site contains an 86,000 square foot warehousing and distribution center and is the primary distribution facility for Sanofi Winthrop pharmaceutical products to customers, primarily wholesale and hospital accounts both domestically and internationally. The site also serves as the nationwide center for return of outdated, out-of-specification or unused products. There are no manufacturing operations located on the site.

3. Applicable Environmental Regulations

Sanofi Winthrop Incorporated - Des Plaines facility is a hazardous waste generator. During the current contract period, all industrial hazardous waste is transported via JB Hunt Special Commodities, to ENSCO, American Oil Road, El Dorado, AK 71730 for incineration. Non-hazardous waste is brokered to incineration facilities, currently OGDEN Martin of Lake, Florida with an option to use ENSCO and Chambers Medical Technologies of South Carolina, Inc.

1. Hazardous Waste EPA ID Number: ILD 001870179
2. Waste Transport: JB Hunt Special Commodities: EPA ID Number ARD 981908551
3. Disposal Facilities: ENSCO, Inc.: EPA ID Number ARD 069748192

As the facility is a Distribution Center **ONLY**, there are no processes at Des Plaines, and therefore, industrial non-hazardous solid wastes are not disposed at local landfill sites, nor are there any wastewater or air emission permit regulations.

● Location Where the Product Will Be Used

The drug product is intended for the use in and will be distributed to the hospitals, private doctors offices and pharmacies throughout the United States.

- **Locations Where the Product Will Be Disposed**

Under the Sanofi Winthrop, Inc. Guaranteed Sales program, out-of-specification, unused or outdated drug product may be returned to the Des Plaines, Illinois facility for disposal. Quantities returned to the Des Plaines facility will be shipped to licensed facilities for disposal by incineration according to applicable environmental regulations. Hospitals and offices may also dispose of the drug product as part of their medical waste stream.

3.4.5 Identification of Chemical Substances that are the Subject of the Proposed Action

- Description of the Drug Substance

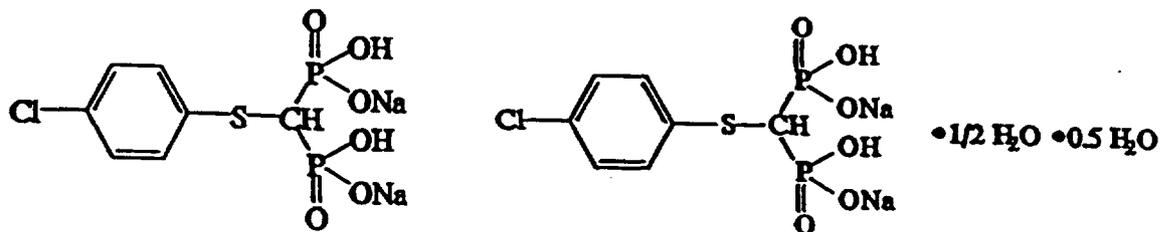
USAN:	Tiludronate disodium
CAS:	Phosphonic acid,[[[4-chlorophenyl]thio]methylene] bis-, disodium salt
CAS:	Phosphonic acid,[[[4-chlorophenyl]thio]methylene] bis-, disodium salt, hydrated hemihydrate*
IUPAC:	[[[4-Chlorophenyl]thio] methylene] bis[phosphonic acid], disodium salt hydrated hemihydrate*
INN:	[[[p-chlorophenyl]thio] methylene] diphosphonic acid, disodium salt hydrated hemihydrate*
Synonyms:	Disodium dihydrogen [[(p-chlorophenyl)thio]methylene] diphosphonate; disodium tiludronate
CAS Number:	149845-07-8 (anhydrous) 155453-10-4, 7732-18-5 ¹ (hydrated hemihydrate)*
Internal code:	SR41319B
Molecular weight:	362.6 (anhydrous tiludronate disodium) 380.6 (hydrated hemihydrate tiludronate disodium) ²
Empirical formula:	C ₇ H ₇ ClNa ₂ O ₆ P ₂ S (anhydrous form) C ₇ H ₇ ClNa ₂ O ₆ P ₂ S•½H ₂ O•0.5H ₂ O (hydrated hemihydrate form)
Physical description:	White to off-white powder

*Tiludronate disodium is synthesized as the hydrated hemihydrate

¹ The hydrated hemihydrate of the form of tiludronate disodium is represented by two CAS registry numbers. The 155453-10-4 represents the originally registered hemihydrate structure which was subsequently revised to the currently registered hydrated hemihydrate structure represented by 155453-10-4, 7732-18-5.

² This is a revised CAS structure. The original CAS structure was the hemihydrate form with a molecular weight of 371.6 indicating only one ½ mole of water of crystallization. Several earlier reports may refer to this original hemihydrate form instead of the current hydrate hemihydrate form containing two ½ moles of water.

Structural formula:



Anhydrous Form
USAN Structure

Hydrated Hemihydrate Form
CAS Structure

Physical chemical data:

Bulk Density: about 0.3 to 0.6 g/ml

Density: 1.92 g/ml

Melting Point: 220-260°C

Vapor pressure at 40°C: $<5 \times 10^{-6}$ Pascals

Solubility in water: about 136-138 g/l

Solubility in alcohol: <0.1 g/l

Partition coefficient octanol/water: $\log K_{ow} < -3.8$

UV visible absorption: 264 nm (buffer pH=4.8); 266 nm (buffer pH=9)

Dissociation constant: 10.85 (pK1); 6.90 (pK2); 2.95 (pK3); 1.30 (pK4)

Health & safety:

Sanofi Health Protection Guideline (SHPG): 0.33 mg/m³ (TWA)

Dust explosion minimum ignition energy: >500 mJ

Thermal stability: $>400^\circ\text{C}$

Toxicity:

LD₅₀ Oral rat: 430 to 700 mg/kg

LD₅₀ Oral mouse: 1200 to 1400 mg/kg



MATERIAL SAFETY DATA SHEET

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Sanofi Winthrop, Inc.
Sanofi Research Division
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

For Emergency Information, call (610) 889-8911
For Technical Information, call (610) 889-8687

Approval Date: October 23, 1996

Substance Name: Tiludronate disodium

Chemical Name: [(4-chlorophenyl)thio]methylene] bis(phosphoric acid), disodium salt hydrated hemihydrate

Synonyms: SR 41319B, tiludronic acid (di)sodium, disodium tiludronate, Skelid

Intended Use: Long-term oral dose therapy of Paget's disease of bone and post-menopausal osteoporosis.

For use within Sanofi Research Division. Prior approval by Health, Safety and Environmental Affairs is required for distribution of this MSDS to anyone other than a Sanofi Research Division employee.

2. COMPOSITION / INFORMATION ON INGREDIENTS:

<u>Component(s)</u>	<u>Weight %</u>	<u>CAS #</u>	<u>SR#</u>	<u>Exposure Guideline</u>
Tiludronate disodium	100	149845-07-8 (anhydrous) 155453-10-4, 7732-18-5 (hydrated hemihydrate)	SR 41319B	0.33mg/m ³

3. HAZARD IDENTIFICATION:

Hazard Codes: (see description last page)

I:2 D:2 F:1 C:1

Hazard Summary:

Health:

Chemical/Physical

x combustible

4. FIRST AID MEASURES

Signs and Symptoms:

Inhalation: Remove to fresh air. If person is not breathing, give artificial respiration. If breathing is difficult, administer oxygen. Seek medical attention immediately.

Eyes: Flush with water for at least 15 minutes. Seek medical attention immediately.

Skin: Flush area with large amounts of water for 15 minutes while removing contaminated clothing. Use soap if available. Seek medical attention immediately.

Ingestion: Consume large amounts of water. Never give anything by mouth to an unconscious person. Seek medical attention immediately.

Note to Physician: Not determined.

5. FIRE AND EXPLOSION PROPERTIES / FIRE FIGHTING MEASURES

Prevention of Fire and Explosion:

Minimize dust generation and accumulation. Keep away from heat, sparks and open flame. Refer to NFPA 654, "Prevention of Fire and Dust Explosions in the Chemical, Dye, Pharmaceutical and Plastics Industries."

A. Dust Explosion Risk:

A/B Classification: Group A (flammable)

Combustibility tests indicate the material burned producing a very large orange flame with no pressure evident.

Minimum Ignition Energy (MIE): 500mj

Take adequate precautions; finely divided solid materials (dusts and fines), when dispersed in the air, can fuel particularly violent and destructive explosions. This material presents an electrostatic discharge hazard.

B. **Thermal Stability:** Not determined.

C. **Electrostatic Risk:** Not determined.

D. **Special Fire-Fighting Procedures:** Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes. Use water spray to keep fire exposed containers cool.

Hazardous Combustion Products: May contain oxides of carbon, sulfur and hydrogen chloride.

Means of Extinction: Water spray, carbon dioxide or dry chemical

6. ACCIDENTAL RELEASE MEASURES

Prevention:

To minimize hazards from accidental breakage of containers, substance should be transported or stored within secondary containers, pans or trays to contain spillage and simplify cleanup. Use protective coatings and/or barrier sheeting in use areas where possibility of spillage exists to simplify cleanup.

Response:

If a small spill occurs, wipe up spill with moistened cloth and place in an impervious container. Wash the contaminated area with a suitable solvent or water plus a surfactant if necessary. Place waste container inside an outer container and remove from the isolator or safety cabinet to a labeled container marked for disposal (see section 13).

During a large spill/release emergency, evacuate non-essential personnel from the area. Wear protective equipment to prevent inhalation or eye/skin contact [see section 8]. Minimize dust generation by using a HEPA filter vacuum to clean spillage. If not available, use water/dilute solution of surfactant to dampen the spilled substance before collecting. Gently scoop up and place into suitable impervious container for disposal [see section 13]. Wash spillage area with surfactant and water. Remove any contaminated clothing, personal protective equipment and barrier sheeting, and place in a double sealed waste container.

7. HANDLING AND STORAGE PRECAUTIONS

Only Authorized and Trained Personnel Shall Handle This Compound.

Keep container closed and protect from contamination. Store in a cool, dry place. Store and transport within secondary containers, pans or trays.

Do not breathe airborne substance, and do not allow contact with eyes, skin or clothing. Use only with containment or isolation facilities and equipment, personal protective equipment and safe work practices. Wash thoroughly after handling [see section 8].

Label all containers with hazard information.

8. SPECIAL PROTECTIVE MEASURES

- A. **Exposure Limits:** The substance is expected to be a moderate toxic hazard. Sanofi Exposure Guideline: 0.33mg/m³.
- B. **Preventive Measures:** Restrict access to the work area and take precautions to contain material within restricted area. Implement appropriate work practices and procedures to eliminate exposure.

Small quantities may be handled on the open bench only if there is no potential for generating airborne contaminants. Otherwise, containment (e.g., fumehood) must be used. Wear safety glasses, gloves and a laboratory coat.

Large quantities where there is a high potential for generating airborne contaminants must be handled in containment. If containment is not practical then facility controls and personal protective measures (e.g., gloves taped to disposable Tyvek™ suits, air supplied suit) may be necessary.

For operations requiring prolonged or repeated handling, double gloves and skin cover should be worn. Work only in accordance with chemical hygiene plans and instructions for safe handling during both normal and emergency operations. Wash thoroughly immediately after use. Contain and control the emissions from experiments, and properly dispose of wastes generated.

- C. **Ventilation:** Use contained process enclosures, local exhaust ventilation or other engineering controls to maintain aerosols below the exposure limit. All operations must be performed in rooms with negative ventilation.
- D. **Respiratory Protection:** If engineering controls cannot maintain airborne concentrations below exposure limits respirators should be worn. Respiratory protection must be in compliance with the OSHA Respiratory Protection Standard, 29 CFR 1910.134.
- E. **Eye Protection:** Special protection is required to protect employees from exposure to dusts, mists, aerosols, splashes and contact. Wear safety glasses with side shields, a full-face shield or full-face respirator as appropriate.
- F. **Hand Protection:** Wear impervious chemical resistant gloves (e.g. nitrile). Clean gloves inside the containment device to prevent lab contamination. Double gloves should be used when in contact with drug substance.
- G. **Recommended Decontamination Facilities:** An eye wash, safety shower and washing facilities shall be available in the immediate area.
- H. **Medical Conditions Aggravated:** May aggravate renal disorders, gastric disorders or hypoparathyroidism. Abnormal responders may also include those taking NSAIDS.

9. PHYSICAL AND CHEMICAL PROPERTIES

Molecular Formula: $C_7H_7ClNa_2O_6SP_2S$ (anhydrous form)
 $C_7H_7ClNa_2O_6SP_2S \cdot 1/2H_2O \cdot 0.5H_2O$ (hydrated hemihydrate)

Molecular Weight: 362.6 (anhydrous)
380.6 (hydrated hemihydrate)

Physical Description: White to off white crystalline powder

Melting Point (°C): 220 - 260

Vapor Pressure (Pascal): $<5 \times 10^{-6}$ at 40°C

Solubility in Water (@ 20 °C): About 136 - 138 g/L (very soluble)

Partition Coefficient (octanol/water): $\log K_{ow} = -3.8$ (low, not expected to absorb into soil compartment)

Bulk Density (g/cm³): 0.4 to 0.6

Dissociation Constant (pK): 10.85(pk₁), 6.90(pk₂), 2.95(pk₃), 1.30(pk₄)

Hydrolysis Rate (t_{1/2}): Essentially stable

UV/Visible absorption (nm): 263 (Lambda max 0.04 M Acetate/0.2 M NaCl pH 4.8)
266 (Lambda max 0.04 M Borate/0.2 M NaCl pH 9.0)

Soil sorption/desorption (K): 104-363 (Non-mobile compound in soil)

(K_{oc}): 11544-24227
(K_{ow}): 6494-13977

10. STABILITY AND REACTIVITY

Thermal Stability: See section 5.

Incompatibility: Incompatibility of this material has not been investigated. As a precautionary measure, keep away from ignition sources including electrostatic charge, heat, sparks and flame. Keep from contact with oxidizing materials, highly oxygenated or halogenated solvents and organic compounds containing reducible functional groups.

11. TOXICOLOGICAL PROPERTIES

Toxicological properties have not been thoroughly investigated. Unless otherwise stated, a suspension containing tiludronate drug substance was tested.

- A. **Effects of Acute Exposure:** Following single dose administration pharmacological effects associated with altered bone turnover (decreased serum alkaline phosphatase and excretion of hydroxyproline in urine) may be observed. Adverse effects observed in healthy male volunteers include elevation of serum creatinine concentration, changes in brush border enzymes and protein resorption (suggestive of a proximal tubule reaction) in healthy male volunteers.

Dust from tablets is expected to be a moderate toxic hazard following inhalation, ingestion, skin or eye exposure. Based on irritancy studies in the rabbit, dust is expected to be a slight skin irritant and moderate eye irritant.

Toxicity Data:

<u>Route</u>	<u>Test</u>	<u>Species</u>	<u>Results</u>
Oral	LD ₅₀	rat	430-700 mg/kg
		mouse	1200-1400 mg/kg
Intravenous(solution)	LD ₅₀	rat	120-175 mg/kg
		mouse	120-175 mg/kg

- B. **Effects of Chronic (Repeated) Exposure:** Pharmacological effects associated with altered bone turnover include decreased serum alkaline phosphatase and urinary hydroxyproline. Gastrointestinal effects (abdominal pain, loss of appetite, nausea and diarrhea) are the most frequently reported adverse events following repeated administration in the clinic. The Incidence of these events are dose related. Dose related renal effects (proximal tubulopathy, discoloration, interstitial tubulonephritis) have been observed in the mouse, rat, dog and baboon. Elevated serum creatine levels and/or BUN and acute renal insufficiency have been observed in the clinic. Severe transient hepatitis, a severe skin reaction, a slight reversible decrease in lymphocyte subpopulations, and headaches have also been observed in patients receiving tiludronate in clinical trials.
- C. **Developmental Toxicity:** No developmental toxicity was observed in the animal studies conducted at doses which did not produce maternal toxicity.
- D. **Reproductive Toxicity:** No reproductive toxicity was observed in the animal studies conducted at doses which did not produce maternal toxicity.

E. **Mutagenicity:**

Toxicity Data:

<u>Test System</u>	<u>Results</u>
Ames (<i>S. typhimurium</i> / <i>E. Coli</i>) test	Negative (± S9 metabolizing system)
<i>In vivo</i> mouse micronucleus test	Negative
<i>In vitro</i> mammalian & non-mammalian cell systems	Negative
DNA repair assay (rat hepatocytes)	Negative
Chromosomal aberration assay (human lymphocytes)	Negative (± S9 metabolizing system)

F. **Carcinogenicity:**

Toxicity Data:

<u>Test</u>	<u>Species</u>	<u>Results</u>
Oral (1.5 years)	Mouse	Negative
Oral (2.0 years)	Rat	Negative

12. **ECOLOGICAL INFORMATION**

Summary: Tiludronate disodium is freely soluble in water with an octanol/water partition coefficient of Log K_{ow} <-3.8. This suggest the compound will migrate to the water compartment.

This product is very stable. The aerobic biodegradation is zero in 28 days, therefore the product is classified as not readily degradable. Tiludronate disodium has shown low to slight toxicity in microbial inhibition toxicity and activated sludge tests.

Oxygen Demand Data:

<u>5-day BOD</u>	
Reference	102 mg/l
1 mg/l	0 mg/l
10 mg/l	0 mg/l
100 mg/l	0 mg/l
1000 mg/l	0 mg/l

Chemical Oxygen Demand and Theoretical Oxygen Demand

COD for SR 41319B = 0.825 mg O₂/mg
 ThOD for SR 41319B = 0.861 mg O₂/mg

Biodegradation: 28 Day BOD = 0% Biodegradation

Photodegradation: Buffered aqueous solution pH 7 = 4.2 hours
 Deionized water = 8.9 hours

Microbial Inhibition Toxicity:

<u>Micro-organism</u>	<u>Minimum Inhibitory Concentration (ppm)</u>
<i>Bacillus cerevs</i>	>1000
<i>Nustoc muscorum</i>	800-1000

<i>Chaetomium globosum</i>	>1000
<i>Penicillium cyclopium</i>	>1000
<i>Azotobacter vinelandii</i>	100-200

Algal Inhibition/Toxicity:

<i>Selenastrum capricornatum</i> 14 days EC ₅₀ :	36.6 ppm
<i>Microcystis aeruginosa</i> 21 days EC ₅₀ :	13.3 ppm

Acute Aquatic Toxicity:

<i>Daphnia magna</i> 24 hour EC ₅₀ :	562 ppm
<i>Daphnia magna</i> 48 hour EC ₅₀ :	320 ppm
<i>Daphnia magna</i> 48 hour NOEL:	247 ppm

Activated Sludge Test: EC₅₀ SR 41319B: >100 mg/l

13. DISPOSAL CONSIDERATIONS

Discharge, treatment or disposal are subject to federal, state and/or local laws. Consider chemical degradation to a less toxic substance or incinerate after dissolving in a compatible waste solvent after collection in an impervious waste container. Contaminated clean up materials and personal protective equipment should be double (e.g., double sealed bags), marked and disposed by incineration. Outer waste containers should be labeled or marked to indicate contents and hazards for safe handling and disposal. Burn in an incinerator operating under applicable regulatory requirements.

14. TRANSPORTATION INFORMATION

IATA Classification: Not regulated as a dangerous good.
DOT (USA shipping name and classification): Not regulated as a hazardous material.
DOT Reportable Quantity: Not assigned.

15. REGULATORY INFORMATION

OSHA chemical hazards (29 CFR 1910.1200): Not applicable.

EPA List of Toxic Chemicals (40 CFR Part 372): Not applicable.

16. OTHER INFORMATION

Hazard label for this substance should state:

"I-2, D-2, F-1, C-1; for research and development purposes only by trained personnel. Properties of this substance have not been thoroughly evaluated. This substance is moderately toxic; danger of very serious, irreversible effects through inhalation, contact with skin or eyes, and if swallowed."

This material safety data sheet is intended for personnel handling this material in research and development. This material is not intended for human therapeutic use in this form.

This information is furnished without warranty, representation or license of any kind, except that it is accurate to the best of Sanofi Winthrop, Inc.'s knowledge or obtained from sources believed to be accurate. Sanofi Winthrop, Inc. does not assume any legal responsibility for use or reliance upon same. Customers are encouraged to conduct their own tests. Before using any product, read the label.

GUIDE FOR SANOFI RESEARCH DIVISION HAZARD CODES

HEALTH HAZARDS:

I = Inhalation Hazards
D = Dermal Hazards

0 = Basically inert
1 = Low hazard - minor, reversible effects
2 = Moderate hazard - may be harmful
3 = Severe hazard - effects may be dangerous
4 = Extreme hazard - effects dangerous at
very low level of exposure

CHEMICAL/PHYSICAL HAZARDS:

F = Fire and explosion hazard

F0 = Basically inert
F1 = Low hazard
F2 = Moderate hazard - combustible
F3 = Severe hazard - flammable, readily ignites
F4 = Extreme hazard - very flammable

C = Reactivity hazard

C0 = Basically inert
C1 = Low hazard
C2 = Moderate hazard - heat sensitive,
decomposes when heated
C3 = Severe hazard - decomposes
violently when heated
C4 = Extreme hazard - decomposes very
violently when heated

Additional comments: Indicate special hazard consideration

U = Unknown

E = Eye Hazard

● Description of the Drug Product

USAN: Tiludronate disodium

CAS: Phosphonic acid, [(4-chlorophenyl)thio)methylene] bis-disodium salt
Phosphonic acid, [(4-chlorophenyl)thio)methylene] bis-disodium salt, hydrated hemihydrate

IUPAC: [(4-chlorophenyl)thio]methylene diphosphonic acid hemihydrate disodium salt

INN: [(4-chlorophenyl)thio]methylene]bis-phosphonic acid hemihydrate disodium salt

Synonyms: Disodium dihydrogen [(p-chlorophenyl)thio]methylene] diphosphonate

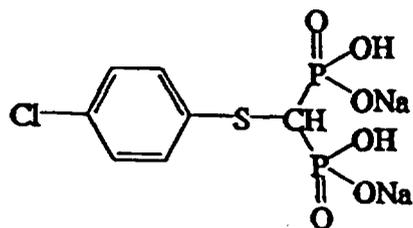
CAS Number: 149845-07-8 (anhydrous)
155453-10-4, 7732-18-5 (hydrated hemihydrate)

Internal code: SR41319B

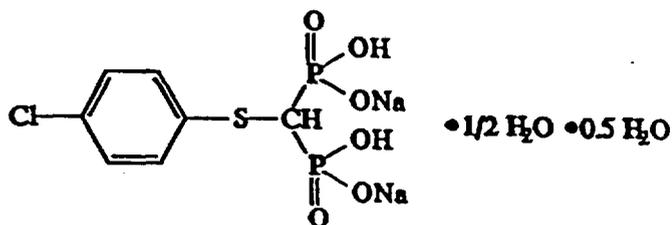
Molecular weight: 362.6 (anhydrous)
380.6 (hydrated hemihydrate of tiludronate disodium)

Empirical formula: $C_7H_7ClNa_2O_6P_2S \cdot \frac{1}{2} H_2O \cdot 0.5 H_2O$

Structural formula:



Anhydrous Form
USAN Structure



Hydrated Hemihydrate Form
CAS Structure

Physical chemical data:

Bulk Density: about 0.3 to 0.6 g/ml
Relative Density : 1.92 g/ml
Melting Point: 220-260°C
Vapor pressure at 40°C: 5×10^{-6} Pascals
Solubility in water: about 136-138 g/l
Solubility in alcohol: <math>< 0.1</math> g/l
Partition coefficient octanol/water: $\log K_{ow} < -3.8$
UV visible absorption: 263.5nm (buffer pH=4.8)
266nm (buffer pH=9)
Dissociation constant: 10.85 (pK1); 6.90 (pK2); 2.95 (pK3); 1.30 (pK4)

Health & safety:

Sanofi Health Protection Guideline (SHPG): 0.33 mg/m³ (TWA)
Dust explosion minimum ignition energy: > 500 mJ

Thermal stability: > 400°C

Toxicity: LD₅₀ Oral rat: 430 to 700 mg/kg
LD₅₀ Oral mouse: 1200 to 1400 mg/kg

3.4.6 Introduction of Substances into the Environment

The production of tiludronate disodium drug substance and drug product will utilize the same facilities currently being used for the production of other pharmaceutical products. For this assessment, engineering estimates are used to predict anticipated discharge levels; however, the evaluations do not reflect changes in treatment process or technology that might be implemented before actual approval of the tiludronate disodium.

Tiludronate disodium drug substance will be produced at Aramon, France. Tiludronate disodium (SKELID) drug product (tablets) will be produced at Ambares, France. The following evaluations of the anticipated environmental impact of tiludronate disodium drug substance is based on total fifth year projected production of tiludronate disodium and on existing environmental control systems at the production facilities.

- **Introduction from Production of Drug Substance at Aramon**

1. **Synthetic Route and Descriptive Summary: *Confidential***

2. **Emissions from the Manufacturing Cycle**

The operations are conducted according to the written instructions of the master record, and throughout the operations, the operating parameters are checked at regular intervals and noted on the batch records.

D. Impurities

The impurities from the manufacturing cycle are not present in environmentally significant levels.

E. Occupational Safety and Health

Personnel in chemical production facilities are provided with appropriate personal protective equipment such as safety glasses, safety shoes, protective gloves/clothing and respiratory protection.

Employees are trained in proper operation of equipment to minimize potential safety, health or environmental risks and in emergency situations. Monitoring of exposure to hazardous materials is routinely conducted. Material Safety Data Sheets are available on-site for all the chemicals handled in the plant.

4. Manufacturing Process: Confidential

5. Compliance with Regulations

A. Statement of Compliance

Sanofi Chimie, Aramon, France will operate within its permit conditions during the production of tiludronate disodium.

- **Introduction from Production of Drug Product at Ambares**

1. Formulation Process

The product formulating process includes receiving, storage, sampling, weighing, granulation, compression, packaging and shipping of the drug product.

The following is a list of the chemicals, commercial products and wastes associated with the formulation of the drug product:

Formulation Constituents: Tiludronate disodium SR41319B
Other materials: *Confidential*

Nonhazardous Wastes:

Shipping containers

Packaging

Out-of-specification SKELID which cannot be reprocessed

Described below, for the three primary ecosystems (atmospheric, aquatic and terrestrial), are the potential emissions for the production of the drug product and their predicted impact on compliance with environmental and occupational health and safety regulations and permits.

2. Emissions from Formulation Operation

A. Air Emissions

Potential emissions are particulate (dust) from the weighing, sampling, granulation (associated with the mixing, drying and calibrating operations) and compression phases. Emissions will be controlled by dust collectors.

B. Aquatic Compartment

During the granulation phase, aqueous streams containing residual amounts of material are released into the residual water during the cleaning operations. This stream is collected and released in the collective purification system prior to discharge to the Ambares Municipal Wastewater Treatment Plant.

C. Waste

Solid waste is comprised of the following:

- Packaging
- Clean packaging

3. Compliance with Regulations

A. Occupational Safety and Health Compliance

Occupational Safety and Health Policy is managed in compliance with all applicable regulations. The formulating and packaging operations are frequently monitored by the authorities in charge of health, safety programs to demonstrate compliance with administrative policies, laws and application decrees.

Personnel in formulation and packaging facilities are provided with appropriate personal protective equipment such as safety glasses, safety shoes, protective gloves/clothing and respiratory protection. Employees are trained in proper operation of equipment to minimize potential safety, health or environmental risks and in emergency situations. Monitoring of exposure to hazardous materials is routinely conducted. Material Safety Data Sheets are available on-site for all the chemicals handled in the plant.

Out-of-specification tiludronate disodium product and formulating process related wastes are minimal hazards to human health. The drug product is stored in closed containers and packages using enclosed systems. Recommendations contained in the MSDS's will be adhered to for the safe handling of all constituent contaminated non-hazardous waste generated during the formulation of the drug product.

B. Statement of Compliance

Sanofi Winthrop, Ambares, France will operate within its permit conditions during the production of tiludronate disodium.

● Emissions from Use

Distribution of the drug product will be undertaken from the Sanofi Pharma distribution center, France to the Sanofi Winthrop, Inc. main distribution center in Des Plaines, Illinois where distribution to the United States will then occur.

Under the Sanofi Winthrop, Inc. Guaranteed Sales program, out-of-specification, unused or outdated drug product may be returned to the Des Plaines, Illinois facility for disposal. Quantities returned to the Des Plaines facility will be disposed of via the municipal waste treatment systems in accordance with environmental regulations.

The Des Plaines facility is a hazardous waste generator, EPA ID Number ILD 001870179. All hazardous waste is transported to a permitted incineration facility and incinerated.

Returned goods are treated to a product reclamation process. During the reclamation process, the drug product is removed from the packaging and the packaging is disposed of in an approved, off-site municipal solid waste landfill.

The drug product will be distributed to clinics and pharmacies throughout the United States and its territories. The primary route of entry into the environment is projected to be via human excretions.

Metabolism studies indicate there is no significant evidence of drug product transformation in human male subjects and rats. This would indicate that the drug product will enter into Publicly Owned Treatment Works (POTW) in an unmetabolized form. The low vapor pressure and high water solubility characteristics for the drug substance indicate unmetabolized drug substance will remain in the water compartment with no migration to the atmospheric compartment. A calculation of the Maximum Expected Emitted Concentration (MEEC) to the aquatic compartment per the CDER Guidance for Industry for the Submission

of an Environmental Assessment in Human Drug Applications and Supplements, November 1995 (CDER EA Guidance Document) indicates an environmental concentration of less than one part per billion (ppb).

- **Emissions from Disposal**

Since wastes from pharmaceutical production and distribution are disposed at incineration and landfill facilities regulated by the EPA or State agencies which consider environmental impacts from waste disposal, the Expected Introduction Concentration (EIC) does not need to be calculated.

3.4.7-11 Environmental Fate and Effects of the Substances Introduced into the Environment Use of Energy and Resources, Mitigation Measures, and Alternatives to the Proposed Action

Pursuant to 21 CFR 25.31a(a) and CDER EA Guidance Document, EA format items 7, 8, 9, 10, and 11 are not necessary for drugs which enter the environment (MEEC) at less than a one part per billion (ppb) "Tier 0" concentration.

3.4.12 List of Contributors and Preparers

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3.4.13 Certification

The undersigned certified that the information presented is true, accurate and complete to the best knowledge of the department responsible for the preparation of the environmental assessment.

Marcel Pointet For MARCEL POINTET

Marcel Pointet
Director, Environmental Affairs
Sanofi Chimie

Dec 4, 1996
Date

3.4.14 References

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